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In Remembrance of Dr. Mary Jeanne Kreek

Dr. Kreek passed away on Saturday March 27, 2021.

To say the least, Dr. Kreek was a remarkable and brilliant person with extraordinary energy. Along with Dr. Vincent Dole and Dr. Marie Nyswander, Dr. Kreek left an indelible mark that changed the lives of millions of people for the better.

Mark W. Parrino, M.P.A.
AATOD President

Dr. Mary Jeanne Kreek presenting the Nyswander/Dole "Marie" Awards at the 2010 AATOD Conference in Las Vegas, Nevada.

THE ROCKEFELLER UNIVERSITY

Office of the President | March 28, 2021

Dear colleagues,

It is with great sadness that I share the news that Mary Jeanne Kreek, a beloved colleague and pioneering physician-scientist, passed away last night. Mary Jeanne was the Patrick E. and Beatrice M. Haggerty Professor and Head of the Laboratory of the Biology of Additive Diseases, as well as Senior Physician at the Rockefeller University Hospital. Mary Jeanne was a pioneer in the biology of addiction research and made seminal contributions that led to methadone's successful use as a treatment for heroin addiction. Beyond her scientific endeavors, she was a champion for her patients, often speaking out against the societal stigma they faced. And of course we all know her passion both for Rockefeller and for the breadth of biomedical science. Her unfailing attendance at Friday Lectures and other campus events, punctuated by incisive questions drawn from her long history in biomedicine, as well as her optimism and unwavering support for women in science are qualities we will not forget.

After graduating from Wellesley College, Mary Jeanne earned her MD degree from Columbia University College of Physicians and Surgeons. During her residency in internal medicine at what is now Weill Cornell Medical School, she first set foot on Rockefeller's campus for a research elective in Vincent Dole's lab, who was investigating the potential use of methadone in the treatment of heroin addiction. After residency she moved to Rockefeller in 1964 as an Associate Physician at the Rockefeller University Hospital to pursue these studies on addiction, and performed early studies with both Dole and Marie Nyswander that led to the hypotheses that addiction was a metabolic disorder in which addicts' brains are functionally altered, and that methadone could help mitigate the symptoms of addiction. In 1966, the trio published one of their first landmark papers showing that methadone could be used to fight heroin abuse.

This early success, large as it was, was only the beginning for Mary Jeanne. By the 70s, she had developed the first laboratory techniques for measuring methadone and similar drugs in blood and tissues. This contribution helped make possible the FDA's approval of methadone for opiate addiction. Mary Jeanne's research also facilitated the development of another drug, buprenorphine, which acts on the same receptor in the brain.

Mary Jeanne went on to become one of the first to document how drugs of abuse significantly alter gene expression in certain brain regions, resulting in neurochemical and behavioral changes. Developing animal models for addiction, and identifying many of the genes and biological pathways that act in concert to increase a person's likelihood of suffering from addiction were among Mary Jeanne's accomplishments. In recent years, her lab identified more than 100 genetic changes associated with addiction, some of which were also associated with atypical stress responses, findings that suggest a predisposition to become addicted.

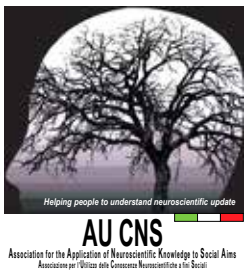
Mary Jeanne has been recognized with numerous awards for her research, including the Betty Ford Award for impact on the field of alcohol and drug abuse in 1996; the Specific Recognition Award for Research in the Science of Addiction from the Executive Office of the President of the United States in 1998; the R. Brinkley Smithers Distinguished Scientist Award from the American Society of Addiction Research, and Nathan B. Eddy Memorial Award from the College on Problems of Drug Dependence, both in 1999; the Wellesley College Alumnae Achievement Award in 2012; and the Lifetime Science Award from the National Institute on Drug Abuse of the National Institutes of Health in 2014. She was the recipient of honorary degrees from Uppsala University, Sweden (2000), the University of Tel Aviv (2007), and the University of Bologna (2010).

In 2017, Mary Jeanne was interviewed for an oral history of her life that included a short film distilled from those interviews, available at this link.

Mary Jeanne will be remembered both for her dynamism as a scientist and her humanism as a physician, patient advocate, and mentor. Please join me in extending our community's deepest condolences to Mary Jeanne's family. She is survived by her two children: Her daughter Esperance Schaefer, with son-in-law Karl Welday and grandchildren Robert and Francine; and her son Robert Schaefer, with daughter-in-law Heather Fain Schaeffer and grandchildren Meryl and William.

Sincerely,

Rick Richard P. Lifton, M.D., Ph.D.
Carson Family Professor
Laboratory of Human Genetics and Genomics
President
The Rockefeller University



Heroin Addiction and Related Clinical Problems

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About Us

EUROPAD, formerly EUMA, was founded in Geneva, Switzerland on September 26,1994. It is, and shall remain independent of political parties and of any government. EUROPAD currently has around 1900 members (HARCP registered readers).

The Vision

EUROPAD exists to improve the lives of opiate misusers and their families and to reduce the impact of illicit drug use on society as a whole. The association works to develop opiate addiction treatment in Europe but also aims to make a major contribution to the knowledge of, and attitudes to, addiction treatment worldwide.

To achieve this vision EUROPAD seeks to:

- Extend the provision and quality of treatment services to drug abusers and their families, especially heroin addicts.
- Promote the development and acceptance of substitution therapy including long term prescribing.
- Help the general public, their elected representatives and officials to understand and accept substitution prescribing in particular and addiction treatment in general.
- Encourage and support research into the effective treatment of opiate addiction and facilitate the communication of research results particularly through its journal- Heroin Addiction and Related Clinical Problems, the EUROPAD web site and the associations conference programme.
- Develop a European network to facilitate communication and co-operation among individuals and organisations working in addiction treatment services throughout Europe.
- Build an International network of "partner" societies and organisation to enable Europe to play its part in the continuing development of opiate addiction treatment. Build an International network of "partner" societies and organisation to enable Europe to play its part in the continuing development of opiate addiction treatment.

EUROPAD seeks to obtain financial support from government agencies, philanthropic organisations, corporations and any other sources, public or private.

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HEROIN ADDICTION & RELATED CLINICAL PROBLEMS

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Drugs as communication between ego and self. Revisiting C. G. Jung

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"We do not see things as they are.
We see things as we are"
Rabbi Shemuel ben Nachmani,
Talmudictractate Berakhot, 55b.

It is necessary to discover and revisit some of the main theories of the analytical psychology of Carl Gustav Jung in order to understand and facilitate the stabilization of addiction. To some it may seem a gamble, but for too many decades the limits of cognitive-behavioural psychotherapeutic treatments for addiction and the absence of a specific treatment on the subject by Freudian and post-Freudian psychologists have been highlighted. The time has come to shift the focus of research: from the disease to the person and, therefore, from the search and validation of the diagnosis (as if it were an on/off switch) to the in-depth study of the inner world of the subject, while recognising that the drug does not create anything. It amplifies the inner world and develops imaginative potentials that are already present in the subject, but in a latent, blurred form, stuck between the inner world of the ego and the inner world of the self. This editorial tries to highlight the obvious points of encounter between the concept of self (Selbst) and the psychic state to which the inner world of the addict is directed (so identifying itself).

It is therefore necessary to distinguish clearly between the 'ego' and the 'self' – an essential diversification that makes it possible to attempt an effective stabilization of the psychic state of the addict **[19-21]**. Such stabilization could, in fact, be identified as the primary objective of addiction treatment, and it certainly does not preclude the stabilization of the psychic world of the patient through psychotherapeutic techniques. It is up to the clinician to act fearlessly in order to reconcile the awareness of these two inner worlds in an addicted patient – one built on the foundations of the individual unconscious and the other on the core of the collective unconscious. This editorial has been written as a necessary starting point for a new multidisciplinary approach unifying psychology and psychiatry in the study of addiction.

Currently, society is organized as a function of the "I", or, more precisely, at the service of the 'ego'. The ego is the centre of the conscious mind. Observing the world and contemporary society from this incomplete perspective is on one hand necessary, on the other an unjustified limitation to human and scientific knowledge. The ego responds above all to the dictates

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of individualism, and society itself tends to reward the individualistic and, therefore, subjective concept, since it paradoxically responds better and more immediately to the needs of the masses (as opposed to the needs of the community): in fact, it exalts freedom of expression, movement and compulsive consumption.

Ego-driven behaviour follows two directives: the search for gratification and therefore pleasure, and the avoidance of displeasure and therefore punishment **[23]**. In the brain there are the "gratification centres" that are located in the limbic system (which is the complex of brain structures that originally appeared in lower mammals and whose purpose is the preservation of the individual and the species) **[2-5]**.

As a large body of supporting scientific literature shows, the ego is able to avoid anything that may cause immediate displeasure and is, instead, instinctively attracted to anything that refers to previous experiences of pleasure. The term 'previous' is quite indispensable in this analysis because the ego bases most of its instinctive choices on habit and, therefore, on a type of conscious experience that has become part of the subject's non-declarative memory. Non-declarative memory differs from declarative memory in that it interacts with the unconscious, leaving no trace of its genesis.

In psychology, we speak of non-declarative memory because it depends on the repeated performance of a task (e.g. the ability to play instruments by ear, the acquisition of motor skills such as those specific to sports and dancing). A society addicted to the exaltation of the ego is a society addicted to immediate but, consequently, temporary rewards. As a result, the ego aims to find shortcuts as quickly as possible that can guarantee a conspicuous and gratifying social position, recurrent erotic satisfaction, economic wealth, and psychophysical well-being that must necessarily be shown to others in order to climb the social pyramid (hence the addiction to social well-being and, therefore, to the spectrum of rewards that often tends to develop, especially in young people). The ego shuns any suffering or pain, which is why it pushes the subject to act for short-term objectives and, unlike the unconscious (especially the self), allows the subject to learn only through the mechanism of gratification.

Carl Gustav Jung (1875-1961), Swiss psychiatrist and psychologist, was the founder of analytical psychology. Already a collaborator of Eugene Bleuler at the Burghölzli psychiatric clinic in Zurich (where he began his first associative experiments), he soon began an intense and prolific collaboration with Sigmund Freud (the first meeting between them took place in Vienna in 1907, whereas the correspondence between them began a year earlier).

Jung was deeply knowledgeable about archaeology, palaeontology, zoology, and biology. He coined the term 'complexes', which has since become universally accepted. In 1910 Jung became the first president of the "International Psychoanalytic Association" in Nuremberg. His publication "Symbols of Transformation" marked the official separation from Freud, mainly because in it Jung set out a different theory of the libido **[12]**.

"The real intent of this book," Jung himself wrote in the preface to the second edition (published in 1924), "is only to elaborate as thoroughly as possible all the historical and spiritual factors that flow into the involuntary products of an individual fantasy. In addition to the obvious personal sources, the creative imagination also has at its disposal the long-forgotten and long-buried primitive spirit with its peculiar images manifested in the mythologies of all times and all peoples. The set of these images constitutes the collective unconscious, a heritage potentially present in every individual. It is the psychic equivalent of the differentiation of the human brain. This is the reason why mythological images can be reborn continuously and spontaneously in harmony with each other, not only in all corners of the vast world but also in all times. They are present always and everywhere. It follows, of course, that it is possible to relate the most distinct mythologies in terms of time and ethnicity to a system of individual fantasies. The creative basis is everywhere the same human psyche and the same human brain which, with relatively minor variations, functions everywhere in the same way" **[12]**.

The main reason for the tension between Freud and Jung was a scientific question about the meaning of the libido and its true nature. Freud believed that mental disorders resulted from the suppression of sexuality and that the substitute for erotic interest evolved in a patient's inner world. Jung's view on the subject was that the loss of reality (which is seen in schizophrenia) cannot be explained by the suppression of sexuality alone. This is why Jung uses the term 'libido' to refer to all forms of psychic energy.

For Freud, the unconscious in essence is nothing more than the point where repressed or forgotten meanings converge. Consequently, from this perspective it is of an exclusively personal nature **[15]**. Jung and Freud met personally for the last time in September 1913 at the Fourth International Congress of Psychoanalysis in Munich.

As pointed out by the historian Sonu Shamdasani, Jung did not consider mental illness a phenomenon antithetical to the state of health but believed it should be placed at the extreme end of a continuous spectrum. The pivotal objective of analytical psychology is to integrate into consciousness the "fantastic" figures of the inner world, in order to allow the reactivation of the mythopoetic imagination and, above all, allow the embrace, alliance and collaboration of the spirit of time with the spirit of the deep. Ultimately, it

is a historical requirement to recognise the irrational as an indispensable psychological factor.

Drug addiction has a numinous power. Jung recounts a visit by him to a distillery at the age of fourteen: his description of drunkenness is deeply significant: "there was no more inside or outside, no more 'I' and 'others', personality number one and personality number two were no longer there". As is well known, Jung often spoke of the presence of two dissimilar personalities within himself and, more generally, within each person, the first dominated by reason and the deeper, second one dominated by the unconscious. Jung continues: "prudence and timidity had disappeared and the earth and the sky, the universe and everything that creeps and flies, turns, rises or falls, had become one". He later recalled this experience as "a discovery, a premonition of beauty and meaning".

Rediscovering Jung's scientific thinking is all the more necessary if we talk about drugs, drug addiction and addiction in general, because Jung was the first and only thinker in the field of psychoanalysis to grasp the psychic function of drugs not only as a change of mood (tranquillising or exciting) but, first and foremost, as a shift in what is happening in the inner world. For Vincent P. Dole, addictive substances are those whose consumption does not change according to price, meaning that it is not only money that counts **[6-9]**. Jung was always able to focus on the inner human world and thus on the person, and then concentrate on the disease or addiction. What we are currently witnessing is, above all, the reverse process in the search for a cure: first we diagnose, first we find the psychopathological category to which the subject belongs, and then we go on to study what causes this in his/her inner world. In this way, although the illness acts in a bidirectional way on the patient, that patient is still the subject in whom all the dynamics are modified, and not vice versa. The disease or, more precisely, the sick person (real or hypothetical) is, and must always remain, the object and never change into the subject (who is always the patient with his/her inner world). Jung attributed the true drama of modern man to the loss of connection with the soul. Addiction to the object (drugs) makes the subject 'extroverted' (in reference to Jung's classification of types).

Jung taught us that only by starting from the inner world can we attempt to observe and understand the totality. Drugs therefore need to be labelled correctly: they are 'special objects' capable of upsetting and numbing the boundaries of the inner world of the subject who takes them. This is because drugs act at the deepest level of psychic functioning; it is therefore the unconscious that is their natural battlefield with reason.

Drugs do not create anything; they only bring out the embryonic potential already present in the unconscious of each subject who uses them (otherwise they would create the same responses and produce the same inner images in all subjects).

Here we reach a crucial point: where does the embryonic potential that drugs seem not only to activate but also to develop come from? What is certain is that the correlation between drugs and the deep level of human psychic functioning is very clear. The drug conditions the behaviour of the addict only as a result of the disruption of the subject's inner world and not as a response to external stimuli or behavioural cues linked to the use of previous experience.

When the drug affects the unconscious, by doing so it abolishes divisions, so that fragmented worlds are merged, but the sense of wholeness is illusory; what is left once the effects of the substance wear off is the numinous power of addiction. The encounter with totality and wholeness is, in fact, the 'unmerited satisfaction' of the addict, who will then try by all means, whether licit or illicit, to regain possession of it. Drugs can, in fact, be a quick shortcut, the cognitive bias preferred by the subject without individuation who seeks totality, the completeness of existence or at least the possibility of seeing it, even if only for a limited time. It is as if the drug could help the subject to cross the border between the ego and the self, as if it could allow the subject to be 'satisfied with having understood' (read also: 'satisfied with an awareness of having understood'), but then leaving him/her helpless, unable to return to the state of understanding the wholeness momentarily induced by the toxic substance, without a repetition of the intake of the substance itself.

The term 'individuation' indicates the process which is capable of creating a psychological 'individual', that is, a separate and indivisible unity, a whole **[15]**. Individuation means becoming a single being, and by 'individuality' we mean our most intimate, incomparable and singular peculiarity, becoming ourselves, achieving our Selbst (Self) **[13]**. The addict seeks an encounter with the self, an encounter with totality, because something in drugs has been able to develop the embryonic potential of the subject and thus abolish the boundaries of the ego and superimpose them on those of the self – a far more desirable dimension for every human being. The process of individuation is often confused with awareness of the ego, and in this way the ego is mistakenly identified with the self. If that mistake is persisted in, individuation becomes no more than egocentricity and autoeroticism. The self, on the other hand, encompasses infinitely more than the mere 'ego'. Without understanding that differentiation, the self would lose its unconscious dimension and have exactly the same limits as the ego. Individuation does not, in fact, exclude the world; it includes it **[13]**.

The self not only constitutes the central archetype of Jung's thought, but is also the purpose of life, because it is the most perfect expression of the combination of destinies called the individual **[13]**. The self is also to be understood as an entity above the conscious self; it embraces not only the conscious psyche, but the unconscious psyche too. There is no hope of attaining even an approximate awareness of the self, since, however many things we may become aware of, there will always remain an indeterminate and indeterminable amount of the unconscious, which itself belongs to the Selbst **[13]**.

Some of the main Jungian 'key words' are glossed in **Table 1**.

Opioids can connect the ego with the archetype of the mother. The best-known drugs prepared from opium are heroin and morphine. Heroin is a semi-synthetic drug that is prepared by the double acetylation of morphine (or morphine contained in opium). It was first synthesised in 1874 and marketed as a strong analgesic. It was withdrawn from the pharmaceutical market in 1924 (USA) and 1958 (Europe) due to its addictive potential. The 'quality' of heroin sold on the illicit market varies enormously, particularly in terms of its degree of 'purity'; it is generally found at a concentration of 20-50%. Thanks to recent techniques such as PET (Positron Emission Tomography), which allow the functioning of certain brain areas to be visualised even after the stimulus has been given, it is very useful to focus on how the brain systems respond to externally introduced substances such as morphine and heroin. These brain systems respond primarily to substances that are produced by the body itself and are certainly similar to exogenous substances – endorphins. As is well known, endorphins enable us to see the contiguity between biological and psychological data: one practical example is the system of attachment to the mother **[1]**. If a baby animal is separated from its mother, it shows obvious signs of distress, which disappear if the mother returns. If, instead of bringing the mother back, one wants to eliminate the manifestation of despondency by pharmacological means, various types of drugs can be administered (from benzodiazepines to neuroleptics, including barbiturates), but the only effect that can be sporadically obtained is a certain level of sedation. The substance that, in very small doses, determines the absolute appeasement of the puppy's despondency (in a similar way to the approach of the mother) is morphine. The same action is also carried out by reassuring the desperate mother for the removal of her baby. This, in the manifestations arising from attachment and detachment (therefore with a relational matrix), indicates that the system with which morphine interacts is involved **[18, 22]**.

The fact that the attachment of the natural mother can be replaced (even if within temporal limits) by a substance such as morphine or heroin seems to indicate that at a certain dimension of the self, the self identifies itself with the (primordial) form rather than with the (de facto) image, that is, with the archetype of the mother rather than with the natural mother. Archetypes can, in fact, be reproduced spontaneously at any time and anywhere, independently of external influences. In every psyche there are (unconscious but absolutely active) forms, dispositions, ideas in the Platonic sense, which instinctively preform and influence our thoughts, feelings and actions. They are not, however, determined in terms of content, but in terms of form, and, even then, to a very limited extent. The fact that a primordial image is determined (in terms of content) can only be demonstrated when it has become conscious and has therefore already been enriched with the material of conscious experience. The archetype is in itself an empty, formal element, nothing more than a 'facultas praeformandi', a possibility given a priori of its form of representation. The elements that are inherited are not actual representations, but forms, instead **[16]**. It should be stressed that the view of the mother from a psychoanalytic point of view is very deficient because, on this view, the personal mother is of primary and exclusive importance – a theory that was later partly retracted by Freud himself, who in his maturity asserted instead that the true aetiology of neurosis is not rooted in traumatic events (as he had indicated earlier), but in the personal evolution of infantile fantasies (as a result, that source becomes the child's inner world) **[16]**.

1. Introduction to clinical. diagnostic and therapeutic implications

Jung was the first psychiatrist to grasp the secret of a (lasting) 'stabilisation' of addiction. Addiction always conceals the need for a sense of wholeness. In the case of drugs, as mentioned above, in order to approach the desired sense of wholeness, the addict needs to numb the boundaries between the ego and the self, so as to achieve the satisfaction of awareness, even if that awareness turns out to be only a short-lived, instantaneous experience. Under the acute effects produced by heroin, for example, all the events happening in the outside world are perceived by the subject, but they fail to arouse any interest or involvement. The effects of the drug tend to estrange the user from the outside world, but the sensations produced by the drug completely satisfy the subject's inner world.

It is impossible to separate this sense of wholeness from the numinous power it produces over the individual. This is why drug addiction can also be described as a 'spiritual thirst' that requires a genuine radical conversion to the psychology of Selbst (the self). Thoughts of spirituality lead to thinking about the divine, and science is far from being able to prove

Table 1. Indispensable Jungian glossary

Active imagination	Method of assimilating unconscious contents by experiencing them as fantasies in the waking state
Anima	The archetype of the woman in the man
Animus	The archetype of man in the woman
Anthropos	Primordial man, the archetypal image of wholeness in alchemy, religion and gnostic philosophy
Archetypal image	The form or representation taken by the archetype in dreams, fantasies, cultural and religious (mythical) products
Archetype	Primary structural element of the human psyche: the archetype is pre-existing and has a predetermined form, is present always and everywhere; it governs the functioning of psychic processes
Assimilation	The process of conscious integration of the contents of the personal and collective unconscious. Assimilation is the result of conscious processing (insight) in the psychotherapeutic process
Collective unconscious	Distinct from the personal unconscious, the collective unconscious is made up of archetypes or primordial images
Complex	A group of emotionally charged ideas or images
Individuation	Complex process of synthesizing the self that consists primarily of the union of the unconscious with the conscious
Integrity	Psychic stage in which the union of the unconscious with the conscious has been achieved: this is the goal of Jung's psychotherapy
Numinous	Defines the quality of archetypal images that are capable of inspiring powerful feelings, such as those of panic or devotion
Personal unconscious	The Freudian unconscious, made up of repressed desires, as distinct from the collective (archetypal) unconscious
Self	The archetype of psychic totality
Shadow	Containing repressed parts of the human personality, the shadow is the counterpart of the Freudian unconscious. The shadow is an archetypal feature

the existence of God. What does appear to be scientific, however, is the category of undeniable existence to which the divine sphere belongs – the category of archetypes. Certain ideas appear almost everywhere and at all times and can even take shape spontaneously, independently of migrations and traditions. They are not the work of the individual; he/she is subjected to them; indeed, they impose themselves on individual consciousness. This is not Platonic philosophy, but empirical psychology **[11]**.

Stabilising drug addiction clinically is a complex phenomenon and difficult to label precisely because of the many psychological variations that each drug user presents. The defence mechanisms that emerge during clinical interviews need to be entirely eradicated, and this may require a period of initial acquaintance that may last a few weeks or even several months. It should, however, be made clear from the outset that the main way to attempt a conjunction between the ego and the self is always an archetype. Experiencing as personal qualities the contents of the collective unconscious, in particular the influence of archetypes, means experiencing maximum states of superiority or inferiority, of "Gottähnlichkeit" (God-likeness), as Goethe put it.

The addict generally has to face a barred road in moving from the ego towards the self, and the more addiction to the substance increases, the more the wall between the ego and the self becomes impassable without taking the substance. It is up to the preparation and mental agility of the professional to understand which archetype holds the key to interpretation that stays closest to the history of the person concerned. There are many archetypal forms present in human history, but we will limit ourselves to introducing three that present important correlations, at a sensory level, between the effects of the drug and their descriptive peculiarities.

The mother archetype has particular correlations with the puppy/adult attachment system and morphine intake. The mother is the precondition, the psychic presupposition of the child, and the child initially lives in "unconscious identity" **[16]** with her. With the awakening of the ego, the participation of the unconscious identity slowly dissolves, and the consciousness begins its opposition to the unconscious: the result is the differentiation of the ego from the unconscious identity of the mother. In an addict who has had particularly traumatic experiences in his/her relationship with the mother, it becomes more necessary and urgent than ever to re-establish the function

of the maternal archetype (rather than the physiological mother), and only an adequate exploration of the archetype, associated with the drive for individuation, will, over time, be able to re-establish a link between the ego and the self, by replacing the need for the substance with the archetypal symbol that will allow the subject to 'become' himself/ herself (so creating a link between the ego and the self).

Addiction is inseparable from the numinous aspect: the divine archetype is in fact what has always moved the mind and body of human civilisations, and the psychology of the ego that is so predominant today has relegated the concept of God to the slums of necessity, but in so doing has in fact unleashed even more neurosis in human beings. This is because society has attempted to separate man from his history, from his belonging to the human race, uprooting him from his origins and outlining a dangerous ego psychology that brings obvious idiosyncrasies alongside mental health.

The concept of imago Dei derives from the Fathers of the Church, according to whom it is imprinted in man's soul. According to Jung, when such an image arises spontaneously in dreams, fantasies or even visions, in the context of psychological speculation, it is to be understood as an effective symbol of the self. That the divinity acts on us can only be ascertained through the psyche, but we are not able to separate whether these effects come from God or from the unconscious, i.e. it cannot be established whether the divinity and the unconscious are two different entities: both are limiting concepts for transcendent content. The image of God certainly does not coincide with the unconscious, but rather with a particular content of it, that is, the archetype of the self: it is from this that we are no longer able to separate the image of God **[17]**. The denial, or underestimation, of the archetype of God in an addict (who has experienced ecstatic feelings through substances) reinforces the subject's sense of alienation, as that person has no other effective words or symbols to explain an ecstatic vision except through an archetype that has already been present in the human unconscious for millions of years.

The third, very closely associated archetype is the archetype of the soul. This is because, as Jung says, 'it would be blasphemous to assert that God can manifest himself anywhere except in the human soul itself'. To be precise, the soul must have within it a correspondence with the divine essence, and this correspondence is psychologically formulated by being based on the archetype of the divine image **[14]**.

More specifically, the anima is the personification of a female nature in the unconscious of male subjects, while the animus is the personification of a male nature in the unconscious of female subjects. This 'psychological bisexuality' corresponds to the biological fact that it is the greater number of male (or female) genes that determine the male (or female) gender. The smaller number of genes of the opposite sex seems to contribute to the character of the opposite gender; this component, however, usually remains unconscious, due to its lower potency **[10]**. The man carries within himself an image of a female archetype, not the image of a particular woman, but of a particular type of woman. This image is, after all, an unconscious hereditary whole of very remote origin, grafted on the organic system as a synthesis of all the ancestral experiences of the female soul and all the impressions provided by women, amounting to a system of hereditary psychic adaptation. Since this image is unconscious, it is projected onto the loved one and is one of the main causes of passionate attraction or its opposite **[10]**.

It may happen that the addict rationally explains that the cause of his/her addiction is the unrequited love of a person, and therefore that this disappointment may be the cause of a malaise which later leads to drug addiction. In this case too, the best way to replace the substance with the archetype, with the symbol, is always to become aware of the self through the attempt to enhance communication by bridging the gap between the ego and the self.

Alienation is one of the words most frequently quoted in the clinical literature on drug addiction, and it is our duty to grasp the fact that it is only through symbols that we can avoid feeling foreign.

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The relationship of alexithymia with difficulty in emotional regulation, anxiety, and depression symptoms in a group of patients receiving opioid maintenance treatment

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Summary

Background: The purpose of this study was to evaluate the relationship between alexithymia and emotion regulation difficulties in a group of patients receiving opioid (buprenorphine). **Methods:** The study was directed to the problems of inpatients in the Alcohol and Substance Dependence Service of Bakırköy Mental and Nervous Diseases Training and Research Hospital. Data from 90 patients with opioid use disorders were evaluated. The following scales were adminstered to each of the patients participating: the State-Trait Anxiety Inventory I-II (STAI I-II), Beck's Depression Inventory (BDI), Difficulties in Emotion Regulation Scale (DERS), and Toronto Alexithymia Scale (TAS-20). **Results:** 54.4% of the patients were found to have alexithymia or possible alexithymia. There were no statistically significant differences between those who had alexithymia and those who were free of it in terms of age, years of education, age at first substance use, duration of heroin use, marital status, and employment status. The alexithymic patients scored significantly higher than the non-alexithymic patients on DERS (104.35±16.70 vs. 77.88±12.48, p>0.001), STAI-I (37.69±9.42 vs. 33.15±6.68, p=0.009), and STAI-II (50.10±7.27 vs. 40.20±6.29, p>0.001). The BDI scores (17.81±12.40 vs. 11.31±12.90, p=0.056) did not differ significantly between the two groups. The MANCOVA analysis showed that difficulty in identifying feelings as a subdimension of alexithymia was predicted by trait anxiety and the awareness, strategies, and clarity subscales of DERS, and the externally-oriented thinking subdimension of alexithymia was predicted by the awareness subscale of DERS. Linear regression analysis showed that difficulty in emotion regulation (with special reference to clarity, strategies, and goals subscales), taken together with trait anxiety, predicted the severity of alexithymia. **Conclusions:** Our findings indicate that, in particular, the clarity, strategies, and goal subscales of DERS, along with trait anxiety, are associated with the severity of alexithymia in those with opioid use disorder who are receiving maintenance therapy with buprenorphine.

Key Words: Opiate; buprenorphine; alexithymia; difficulty in emotion regulation; anxiety; depression

1. Introduction

The concept of alexithymia, which is derived from clinical observations in the field of psychiatry and psychosomatic medicine, is a dimensional personality trait distinguished by difficulties in identifying and describing subjective feelings, a limited imaginal capacity, and an externally oriented style of thinking [50]. In 1976 Nemiah, Sifneos, and Freiberger defined alexithymia as a multifaceted construct with the following salient features: difficulty in identifying feelings and distinguishing between feelings and emotional bodily sanctions arousal; difficulty in describing feelings to other people; constricted imaginal processes, as shown by a paucity of fantasy; and a stimulus-bound, externally oriented cognitive style [35]. Whether alexithymia is a long-term/permanent trait or a temporary condition is still unclear [43]. In addition to studies which suggest that alexithymia is a permanent personality trait [32], there are other studies which suggest that alexithymia is both a state and a trait, without being related to

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changes in withdrawal symptoms, including anxiety and depression-like symptoms [9].

The alexithymia rate in the general population is estimated to vary between 7.3 and 10% [20, 29, 33]. Alexithymia has been shown to be associated with various medical and mental disorders [31]. Alexithymia qualifies as one of the significant risk factors for addictive behaviour [14, 53]. Substance-dependent individuals have been found to show higher levels of alexithymic features [40, 41]. In a review of important studies published since 2009, prevalence rates of alexithymia among alcohol-dependent samples were identified as ranging between 30% and 49% [6]. Similarly, individuals with substance use disorder also have high alexithymia rates that range between 35 and 62.8% [10, 13, 16, 21, 27, 44]. Studies show that alexithymia levels in individuals with substance use disorder do not significantly fall even after prolonged periods of abstinence [40].

The salient features of the alexithymia construct reflect a deficit in the cognitive processing and regulation of emotions [49, 51]. Many indirect empirical findings support the presence of difficulties in emotional regulation in alexithymia. The findings of Pandey et al. show that alexithymia is associated with difficulty in emotional regulation, and an overlap is observed between these constructs [37]. Addictive behaviour in alexithymic individuals is believed to be mediated by difficulty in emotional regulation [11]. Several studies have reported that alexithymia is positively correlated with maladaptive styles of emotional regulation (such as binge-eating or drinking alcohol) and negatively correlated with adaptive behaviours such as thinking about or trying to understand distressing feelings or talking to a caring person [37, 38]. It has been stated that several aspects of emotional dysregulation in substance users may relate to alexithymia, which is marked by a reduced ability to identify, define, and/or explain one's own emotions, as well as a tendency to externalize feelings and experiences [34, 48]. Individuals with a high level of alexithymia who are unable to identify their own subjective emotions accurately are limited in their ability to reflect and regulate their emotions, as well as in communicating their emotional distress verbally to others. They therefore fail in any attempt to enlist others as a source of help or comfort. Lack of emotional sharing may also contribute to difficulties in identifying emotions [50].

The regulation of emotions refers to an individual's ability to modify an emotional state to support their adaptive, purposeful behaviour [52]. According to Gratz and Roemer, emotional regulation involves the following: awareness, understanding, and acceptance of emotions; ability to control behaviours when experiencing negative emotions; flexible use of situationally appropriate strategies to modulate the intensity and/or duration of emotional responses, rather than to eliminate emotions entirely; and a willingness to experience negative emotions as part of pursuing meaningful activities in life [22, 23]. A deficit in any of these four areas is interpreted as indicative of emotional regulation disorder. Difficulties in recognizing, understanding, or modulating emotion may interfere with adaptation and lead to negative outcomes [3]. Evidence has been shown that alcohol-substance use disorder is associated with increased levels of difficulty in emotional regulation [18, 19, 24]. Individuals with heroin addiction who are not experiencing physical withdrawal symptoms tend to experience more negative emotions and have fewer cognitive resources at their disposal than individuals with heroin addiction who are experiencing such symptoms [54]. It has been stated that inefficient emotion regulation strategies may lead to craving and the perseverence of alcohol use [39]. On the other hand, higher scores related to alexithymia have been associated with poorer emotional regulation skills, greater alcohol dependency severity, and high-risk drinking situations [47].

Most inquiries into the relationship between alexithymia and addiction focus on individuals with alcohol or multiple substance abuse. To the best of our knowledge, there is no study addressing alexithymia and emotional regulation difficulties in individuals with opiate dependence. The purpose of this study has been to evaluate the relationship of alexithymia with emotional regulation difficulties in a group of patients receiving opioid (buprenorphine) maintenance therapy. We have also aimed to control the effects of depression and anxiety on this relationship. We assumed that in this group of patients alexithymia would be closely correlated with other substance use disorders and be positively associated with various pertinent variables (such as difficulty in emotional regulation, depression, and anxiety). In this study, alexithymia levels were assessed using the Toronto Alexithymia Scale (TAS-20) and difficulties in regulating emotion were assessed using the Difficulties in Emotion Regulation Scale (DERS).

Aim: We have aimed to discuss the overlapping and diverging areas of the subscales of both instruments within the scope of the current literature and to make a contribution to the therapeutic approach to this group of patients.

2. Methods

The study sample: The present study involved inpatients in the Alcohol and Substance Service (AMATEM) of Bakırköy Mental and Nervous Diseases Training and Research Hospital.

2.1. Implementation

The treatment plan for patients diagnosed with opiate use disorder in the AMATEM clinic is carried out within the framework of the Suboxone Administration Guide (SAG) [12] prepared by the same clinic. Depending on the patient's clinical status, buprenorphine treatment is gradually reduced and terminated after 1-2 weeks of detoxification, while the treatment of those eligible for maintenance treatment is carried out with a stabilization dose. The eligibility criteria for maintenance therapy were determined on the basis of the SAG (e.g. those who relapsed after detoxification therapy, those actively using opioids for more than two years, those with a criminal record associated with substance use, those with insufficient social support, those who had previously received maintenance therapy). The participants in the study were selected from among those who were receiving opioid maintenance therapy with buprenorphine. The opiate dependency diagnosis was grounded on clinical examination by a trained interviewer and the Turkish adaptation [4] of the Structured Clinical Interview for DSM-IV [17]. The presence of any form of substance abuse, or of any psychiatric or physical disorder other than opiate dependency was considered an exclusion criterion. All patients who had been stabilized with buprenorphine at the end of the first week were informed about the study. All the patients who were willing to participate in the study were given the instruments used in the study in the second week. Informed consent was obtained from each patient prior to enrolment.

2.2. Sample size

A total of 106 patients receiving opioid maintenance therapy participated in the study. Data from a total of 90 patients were evaluated after eliminating those who had failed to fill out the forms in full, or discarded them.

2.3. Instruments

All the patients who met the diagnostic criteria for substance abuse according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition were evaluated using a semi-structured sociodemographic and clinical information document. In addition to basic sociodemographic data, the document included some clinical variables such as substance use pattern, history of suicide attempts, and self-mutilative behaviour. Additionally, the State-Trait Anxiety Inventory I (STAI-I), State-Trait Anxiety Inventory II (STAI-II), Beck's Depression Inventory (BDI), Difficulties in Emotion Regulation Scale (DERS), and Toronto Alexithymia Scale (TAS-20) were administered to each patient in the study sample.

2.3.1. Toronto Alexithymia Scale (TAS-20)

This Likert-type self-report scale developed by Bagby et al. with the aim of measuring alexithymic features consists of 20 items scored from 1 (strongly disagree) to 5 (strongly agree) [1]. The authors suggested three cutoff scores to distinguish between alexithymic (≥61), borderline (51-60), and non-alexithymic individuals (≥50). The Turkish validity and reliability study of the scale was conducted by Güleç et al. [25]. It has three subscales: difficulty in identifying feelings, difficulty in expressing them and externally oriented thinking. A higher score on the scale indicates a greater level of alexithymia. Total Cronbach's Alpha was found to be 0.78, while Cronbach's Alpha for the subscales was between 0.57 and 0.80. It should be noted that, in the study conducted to determine the cutoff score of the Turkish adaptation of the scale, if researchers wish to work with a non-alexithymic group, they should use <51 as the cutoff score, whereas if they wish to work with an alexithymic group, they should use >59 as the cutoff score [26].

2.3.2. Difficulties in Emotion Regulation Scale (DERS)

The scale developed by Gratz and Roemer conconsists of 36 items under 6 subscales [22]: Lack of emotional awareness (awareness), lack of emotional clarity (clarity), unwillingness to accept certain emotional responses (non-acceptance), lack of access to strategies for feeling better when distressed (strategies), difficulty in regulating behaviour when distressed (impulse), difficulty in engaging in goal-directed cognition and behaviour when distressed (goals). The instructions that accompany this Likert-type self-report scale ask respondents to indicate how often the statements in the form apply to them, with scores ranging from 1 (almost never) to 5 (almost always). While the scale has no cutoff score, higher scores indicate greater emotional regulation difficulties. The scale was adapted to Turkish and tested for validity and reliability by Rugancı and Gençöz [42]. Item 10 in the original form of the scale was removed due to very low correlation (r =0.06) with the whole scale, and another item with the same meaning was included. In this way, construct validity was achieved while maintaining the same number of factors and factor structure. The Turkish version of the scale was found to have a Cronbach's Alpha coefficient of 0.94, which indicates an internal consistency similar to that of the original version. The internal consistency coefficients of the subscales range from 0.75 to 0.90. Test-retest reliability was found to be 0.83.

2.3.3. State-Trait Anxiety Inventory

This inventory was used in the study to assess anxiety levels. The Turkish validity and reliability study of the inventory developed by Spielberg **[45]** was conducted by Öner et al. **[36]**. In that study, Cronbach's Alpha coefficient was found to be 0.89 for state anxiety and 0.81 for trait anxiety. The inventory consists of two separate subscales each comprising 20 questions. The state anxiety scale indicates the level of anxiety at a specific moment in time, whereas the trait anxiety scale assesses the level of anxiety that an individual experiences regardless of their circumstances. The total score range is 20-80 for both scales. Higher scores indicate a high level of anxiety, while lower scores indicate a lower level.

2.3.4. Beck's Depression Inventory (BDI)

This inventory was used to assess the presence and severity of depressive symptoms. The Turkish version **[28]** of the inventory **[2]** shows good validity and reliability. The Cronbach's Alpha coefficient for BDI was found to be 0.90 in this study. BDI is a self-report instrument that assesses depressive symptoms with a total of 21 questions. The highest possible score is 63.

2.4. Data analysis

SPSS 18.0 for Windows was used for the statistical analysis. The variables showed normal distribution according to the results of the Kolmogorov-Smirnov test for normality ($p>0.05$). Student's t test was used to compare groups for continuous variables. Categorical sociodemographic variables were compared using χ^2 statistics. Covariants associated with subdimensions of alexithymia were assessed using the multivariate covariance analysis (MANCOVA). Hierarchical (depression, state and trait anxiety scores, and emotion regulation difficulty) linear regression models were used when the severity of alexithymia was taken as a dependent variable. For all statistical analyses, p values were 2-tailed and $p<0.05$ was considered statistically significant.

3. Results

All of the data collected from a total of 90 patients – 8 women and 82 men – all of them receiving opioid maintenance treatment with buprenorphine were used in the statistical analysis. The mean age of the patients was 26.27±5.76, the mean years of education were 9.45±2.83, the mean age at first substance use was 16.14±4.16, and the mean duration of heroin use was 6.40±4.75. 54.4% had displayed self-mutilative behaviour at least once, and 33.3% had attempted suicide. The mean alexithymia score was 53.47±9.55, the mean DERS score was 92.29±19.90, the mean BDI score was 15.55±12.10, the mean STAI-I score was 35.62±8.55, and the STAI-II score was 45.59±8.42.

54.4% (n=49) of the patients were found to have alexithymia or possible alexithymia when >51 was taken as cutoff score **[26]**. **Table 1** shows the comparison between the groups according to the presence of alexithymia. There was no statistically significant difference between those who had alexithymia and those who did not in terms of age, years of education, age at first substance use, duration of heroin use, marital status, and employment status. The alexithymic patients scored significantly higher than the non-alexithymic ones on DERS (104.35±16.70 vs. 77.88±12.48, respectively, $p>0.001$), STAI-I (37.69±9.42 vs. 33.15±6.68, respectively, $p=0.009$), and STAI-II (50.10±7.27 vs. 40.20±6.29, respectively, $p>0.001$) The BDI scores (17.81±12.40 vs. 11.31±12.90, $p=0.056$) did not differ significantly between the two groups. The alexithymic group scored higher than the non-alexithymic group in all subscales of DERS except for awareness **(Table 1)**.

Covariants associated with subdimensions of alexithymia (trait anxiety, DERS subscales) were assessed using MANCOVA **(Table 2)**. The MANCOVA analysis showed that the difficulty often experienced in identifying the feelings subdimension of alexithymia was predicted by trait anxiety and the awareness, strategies, and clarity subscales of DERS, difficulty in expressing the feelings subdimension of alexithymia was predicted by trait anxiety and the clarity subscale of DERS, and the externally-oriented thinking subdimension of alexithymia was predicted by the awareness subscale of DERS (**Table 2**).

Factors predicting the severity of alexithymia were assessed using hierarchical linear regression analysis (**Table 3**). In the first step, trait anxiety symptom severity was included in the analysis as an independent variable. In the second step, the total DERS score was included as an independent variable, and, in the last step, DERS subscale scores were included as independent variables instead. The linear regression analysis showed that difficulty in emotional regulation (in particular, as shown on the clarity, strategies, and goals subscales) together with trait anxiety, predicted the severity of alexithymia.

4. Discussion

To the best of our knowledge, our study is the first to investigate the relationship between alexithymia and emotion regulation difficulty among heroin users. A high alexithymia or possible alexithymia rate (54.4%) was found (with a TAS-20 score ≥51 taken as the cutoff score) among patients diagnosed with

Table 1. Comparison between the groups according to the presence of alexithymia

	Non-alexithymic N=41		Alexithymic N=49			
	Mean	SD	Mean	SD	T	p
Age	26.27	5.62	26.27	5.94	0.002	0.998
Years of education	9.80	2.94	9.15	2.73	1.044	0.300
Age at first opioid use	19.34	3.79	20.31	4.21	-1.135	0.259
STAI-I (State anxiety)	33.15	6.68	37,69	9.42	-2.671	0.009
STAI-II (Trait anxiety)	40.20	6.29	50,10	7.27	-6.842	<0.001
BDI	12.90	11.31	17.81	12.40	-1.938	0.056
DERS total	77.88	12.48	104.35	16.70	-8.376	<0.001
Non-acceptance	13.20	3.83	18.45	4.96	-5.540	<0.001
Goals	13.17	3.72	18.10	3.89	-6.113	0.001
Impulse	12.39	3.20	17.45	5.24	-5.620	<0.001
Awareness	14.24	3.71	15.67	3.47	-1.888	0.062
Strategies	15.49	3.79	22.39	5.09	-7,364	<0.001
Clarity	9.39	2.33	12.29	3.50	-4.680	<0.001
	N	%	N	&	χ^2	p
Married	11	26.8	12	25.0	0.039	0.844
Employed	15	36.6	11	22.9	1.998	0.158

BDI: Beck's Depression Inventory, DERS: Difficulties in Emotion Regulation Scale, STAI: State-Trait Anxiety Inventory

opioid (heroin) use disorder and receiving buprenorphine maintenance therapy, which is one of the important results of our study. The mean alexithymia score was found to be 53.47. Alexithymia scores range from 44.58 to 57.60 in studies conducted with heroin addicts **[5, 21, 41]**. Our study is consistent with the data obtained in these studies and shows a high rate of alexithymia relative to the general population **[20, 29, 33]**. Additionally, high alexithymia levels found in cases such as alcohol-other substance use disorders and behavioral dependencies such as internet or gambling addiction are also consistent with our findings **[8, 11, 14, 27]**. According to these data, it can be concluded that alexithymia is a very significant factor in the development or maintenance of addictive behaviour.

Another important result of our study is that the DERS and anxiety scores of the alexithymic group were significantly higher than those of the non-alexithymic group, which supports our hypothesis. Moreover, the alexithymic group scored significantly higher than the non-alexithymic group in all subscales of DERS except for awareness. The data obtained provide supporting evidence that alexithymia is associated with emotional dysregulation (EDR). In parallel with our study, Pandey et al. made a comparison be-

Table 2. Covariants associated with subdimensions of alexithymia assessed using MANCOVA

	Dependent Variables	Type III Sum of Squares	df	F	P
Trait anxiety	DIF	67.597	1	6.196	0.015*
	DEF	46.657	1	6.248	0.015*
	EOT	9.034	1	1.043	0.310
Awareness	DIF	49.459	1	4.533	0.036*
	DEF	0.289	1	0.039	0.845
	EOT	83.836	1	9.683	0.003*
Strategies	DIF	128.723	1	11.799	0.001*
	DEF	0.594	1	0.080	0.779
	EOT	10.901	1	1.259	0.265
Clarity	DIF	69.116	1	6.335	0.014*
	DEF	34.817	1	4.662	0.034*
	EOT	0.120	1	0.014	0.907

DIF: Difficulty Identifying Feelings, DEF: Difficulty Expressing Feelings, EOT: Externally Oriented Thinking
a. $R^2 = 0.684$ (Adjusted R2 = 0.647) b. $R^2 = 0.480$ (Adjusted $R^2 = 0.420$) c. $R^2 = 0.248$ (Adjusted $R^2 = 0.162$). State and trait anxiety, depression, and DERS subscales were covariants. The table shows statistically significant covariants only.

Table 3. Variables predicting the severity of alexithymia according to the hierarchical linear regression analysis

		Non-standardized Coefficients		Standardized Coefficients		
				Beta	t	p
	Trait anxiety	0.841	0.082	0.739	10.243	<0.001
	Trait Anxiety	0.414	0.104	0.364	3.982	<0.001
	Difficulty in Emotion Regulation	0.245	0.044	0.511	5.589	<0.001
	Trait anxiety	0.411	0.103	0.361	3.997	<0.001
	DERS_Clarity	0.657	0.212	0.228	3.107	0.003
	DERS_Strategies	0.382	0.152	0.228	2.523	0.014
	DERS_Goals	0.402	0.170	0.191	2.365	0.020

Model 1: F=104.910, df:1, 87, p<0.001, Adapted R^2=0.541,
Model 2: F=86.306, df:2, 86, p<0.001, Adapted R^2=0.660, R^2 Change=0.121,
Model 3: F=44.839, df:4, 84, p<0.001, Adapted R^2=0.666, R^2 Change=0.134

tween alexithymic and non-alexithymic participants based on TAS-20, and found that the alexithymic group scored significantly higher than the non-alexithymic group on all subscales of DERS except for awareness [37]. The authors stated that one reason for the non-significant difference observed in the awareness subscale of DERS-H might be related to the low reliability of this sub-scale. A similar problem was mentioned in the study examining the psychometric properties of the Turkish version of the scale. DERS subscales were compared between participants with high psychological distress and those with low psychological distress. Main group effect was found to account for about 21% to 37 % of the variability in DERS subscales except for the awareness subscale, for which the main group effect accounted for only 6% of the variance [42]. The results of another study conducted with a sample consisting of individuals with mental disorders other than substance use disorders supported the hypothesis that emotional awareness and emotional differentiation mediate the relationship between alexithymia and emotion regulation [7]. However, only the awareness and strategies subscales of DERS were used in this study, which limits the possibility of a healthy assessment.

The main finding of our study is broadly in line with our hypothesis, and it was found that difficulty in emotional regulation (especially as shown on the clarity, strategies, and goals subscales), along with trait anxiety, predicted the severity of alexithymia. We observed that depression and state anxiety did not have any predictive effects on this relationship. Based on the data provided by this study, it can be said that alexithymic individuals experience trait anxiety and have difficulty in understanding emotional responses (clarity), limited access to effective strategies of emotional regulation (strategies), and difficulty in engaging in goal-oriented behaviour while experiencing negative feelings (goals). In the study conducted by Pandey et al., three dimensions of difficulties in emotional regulation, namely lack of emotional clarity (clarity), unwillingness to accept certain emotional responses (non-acceptance), and lack of access to strategies for feeling better when distressed (strategies), were found to be more important than the others in distinguishing between alexithymic and non-alexithmic individuals [37]. Stasiewicz et al. conducted a study with a sample consisting of individuals with alcohol use disorder and found that alexithymia was associated with all subscales of DERS, which differs from our results [47]. When our findings are considered together with these studies, it may be stated that difficulties in understanding emotional responses and lack of access to emotional regulation strategies stand out in predicting alexithymic features in individuals with opiate use disorder.

We identified multifaceted relationships between alexithymia and DERS subscales and other variables. The difficulty often experienced in identifying the feelings subdimension of alexithymia was predicted by trait anxiety and the awareness, strategies, and clarity subscales of DERS, the difficulty expressing feelings subdimension of alexithymia was predicted by trait anxiety and the clarity subscale of DERS, and the externally oriented thinking subdimension of alexithymia was predicted by the awareness subscale of DERS. In line with our study, da Silva et al. identified a relationship between the externally oriented thinking subdimension of alexithemia and lack of emotional awareness in both clinical and non-clinical samples. Again, a significant relationship was found between difficulty in identifying feelings and lack of access to emotional regulation strategies in both samples [7].

The relationship between addiction and alexithymia was best studied in samples consisting of those with alcohol use disorder. Reviews of alcohol use disorders support the relationship between alexithymia and alcohol consumption, and show that high levels of alexithymia are associated with increased severity

of alcohol-related problems [6, 53]. In the review by Cruise and Becerra, it is emphasized that there is an indirect relationship between alexithymia and alcohol problem severity. The authors note that this is mediated by certain psychological drinking constructs (e.g. alcohol expectancy, drinking motives, craving, and alcohol-related intrusive thoughts) and psychological risk factors for the development of alcohol-related problems (e.g. mood and emotional dysregulation, attachment, trauma, and cognitive function) [6]. There are data suggesting that alexithymia might be a pre-existing trait that supports substance use [33] and that high rates of alexithymia among individuals with substance use disorders may be explained by the need to resort to substance or alcohol use to eliminate the emotional dysregulation associated with alexithymia [47]. Information on the relationship between alexithymia and difficulty in regulating emotions in individuals with heroin use as a negative way of coping is important in this respect.

Limitations

Our study has certain limitations. First of all, the lack of a control group consisting of healthy individuals is a significant limitation. Although a limited number of other studies have investigated the relationship between alexithymia and EDR, comparisons with a group of healthy controls could have provided more valuable findings. The self-report nature of the measurement instruments used in the study was a second limitation. Alexithymic individuals are more likely to have problems in evaluating themselves accurately due to difficulties in the cognitive processing of emotions. Thirdly, although the clinical scales were administered when the patients were stable and were being given buprenorphine therapy at standard, neither medication dosage nor additional drugs prescribed for sleep were being controlled, which is a significant limitation. Considering the positive effects of the buprenorphine/naloxone combination on anxiety and depression in both pre-clinical and clinical trials [15, 46], the medication dosage that patients receive may affect the results. Given the studies that found a significant decrease in alexithymia scores with antidepressant therapy [30], buprenorphine therapy may have affected our results.

5. Conclusions

In conclusion, our findings indicate that, in particular, the clarity, strategies, and goals subscales of DERS, along with trait anxiety, are associated with the severity of alexithymia in those who have opioid use disorder and are currently receiving maintenance therapy with buprenorphine. It can be said that alexithymic individuals experience trait anxiety and have difficulty in understanding emotional responses, limited access to effective strategies of emotion regulation, and further difficulty in engaging in goal-oriented behaviour while experiencing negative feelings. Drug use behaviour as an ineffective coping method is a possible problem in individuals with high alexithymia levels who experience difficulties in regulating their emotions due to difficulties in adaptive processes. It is therefore important for individuals receiving opioid maintenance therapy to be aware of these difficulties and to develop modalities for this aspect of the therapy. Given the lack of studies on the subject, we believe that our study will make a significant contribution to the literature.

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Contributors

All authors were involved in the study design, had full access to the survey data and analyses, and interpreted the data, critically reviewed the manuscript and had full control, including final responsibility for the decision to submit the paper for publication.

Conflict of interest

All authors have no conflict of interest.

Ethics

Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Ethics committee has approved the study based on Helsinki Declaration

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Follow-up of serum naltrexone levels after naltrexone implant in Opioid Use Disorder

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Summary

Background: The aim of this study has been to analyse serum naltrexone (NTX) in patients with Opioid Use Disorder (OUD) after they had been treated with a naltrexone implant (NTX-XR), to see if that serum NTX subsequently reached therapeutic levels (≥ 2 ng/ml). **Methods:** 15 OUD patients, during their hospitalization at the Akdeniz University Faculty of Medicine, Alcohol and Substance Abuse Research Application Centre (AMBAUM) between February 2018 and June 2019, had subcutaneous NTX-XR 1000 mg administered to them in 12-week depot form, and their blood serum NTX levels were measured at regular intervals. **Results:** The mean age of the study group, which consisted entirely of males, was 27.53±7.15. The mean blood serum NTX levels after NTX-XR application were found to be 0.51±1.92 ng/ml on the day of administration and 7.88±4.91 ng/ml, 6.76±3.18 ng/ml, 2.75±2.59 ng/ml after the first, second and third months, respectively. During the three months following the administration of the NTX-XR serum, our measurements showed that NTX levels stayed above the theraupetic threshold. Moreover, according to the monthly urine toxicology results, patients tested negative for opioids at the end of each of those three months. **Conclusions:** Therapeutic levels of serum NTX were achieved through NTX-XR. We argue that NTX-XR is likely to be an effective and safe option for the treatment of OUD.

Key Words: Opiate use disorder; Naltrexone implant; Blood levels; Treatment

1. Introduction

Addiction is a chronic brain disease that is distinguished by periods of relapse and remission **[1, 13]**. Opioid Use Disorder (OUD), which is a prominent type of addiction, is a public health problem **[12]** showing increasing frequency that causes considerable work-force and economic losses. It is estimated that there are approximately 15.6 million opioid users worldwide, of whom 11 million are heroin addicts **[15]**. Naltrexone (NTX) has been approved by the U.S. Food and Drug Administration as a potent opioid antagonist for the treatment of OUD **[20]**. NTX plays an important role in the treatment of OUD. It blocks opioid receptors, so preventing the action of opioid derivatives. Orally administered 50 mg NTX blocks the effects of opioid for 24-36 hours, is easy to use, and is well tolerated; in addition, no tolerance develops to opioid receptor antagonism **[16]**. It has been shown that the frequency of relapse falls in response to a regular oral NTX dose of 50 mg daily **[7, 20]**. Low patient compliance with daily oral intake of NTX has led to the development of an NTX formulation with sustained release, namely NTX implant (NTX-XR).

Relapses have been reported to occur less frequently in patients treated with NTX-XR than in those receiving oral NTX or placebo **[11]**. One possible explanation for this outcome is notably poor compliance with a daily medication regimen for oral NTX **[22]**. It has been reported that over half of the addiction patients who had volunteered to receive oral agonist maintenance treatment discontinued it within the first 3 weeks **[19]**.

Blood serum NTX level is reported to be associated with relapses. A serum level above 2 ng/ml is recommended for NTX as the effective therapeutic level. One of the concerns about patients treated with NTX-XR is potential negative outcomes when serum

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NTX levels drop substantially. This decrease may be associated with quitting the treatment and resuming opioid use **[3, 6]**.

Aim: In this study we aimed to retrospectively evaluate the serum NTX levels of 15 OUD patients who were on NTX-XR treatment.

2. Methods

2.1. Design of the study

In the present study, 15 patients diagnosed with OUD according to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) at Akdeniz University Faculty of Medicine, Alcohol and Substance Abuse Research Application Centre (AMBAUM) between February 2018 and June 2019 had subcutaneous NTX-XR 1000 mg administered to them in 12-week depot form, and their blood serum NTX levels were measured at regular intervals. Sociodemographic characteristics, blood NTX levels, and liver function tests (LFT; ALT, AST, and GGT) were determined for all patients by examining their medical records. The inclusion criteria in the study were: being between the ages of 18 and 65, having completed the detoxification treatment for OUD after having been started on NTX-XR, and having the blood serum NTX level measured once a month for 3 months. The exclusion criteria were: having a history of neurological disease(s) and mental retardation, pregnancy, active skin infection at the implantation site, hypersensitivity to naltrexone, and active liver disease. Blood serum NTX levels were measured on the day when the NTX-XR implant was put in place ('naltrexone0') and then by the end of the following three months (i.e. the first month (naltrexone1), the second month (naltrexone2), and the third month (naltrexone3)). Additionally, LFT measurements were performed at the same time and then at intervals concomitantly with NTX-XR serum measurements (i.e. AST0, ALT0, and GGT0 at the first month; ALT1, AST1, and GGT1 at the second month and ALT3, AST3, and GGT3 at the third month). Urine toxicology screening was performed too for 3 months in the study group.

This study was approved by the Akdeniz University Faculty of Medicine Clinical Research Ethics Committee (dated 08.01.2020).

2.2. Sample

The present study included 15 patients diagnosed with OUD (mean age, 27.53 ± 7.15 years; all the patients were male). Additionally, all patients were smokers. The sociodemographic characteristics of the patients, including marital status, educational status, disease duration, history of infectious disease(s), forensic events, self-mutilation history, history of substance use treatment, concurrent use of psychiatric drugs, average opioid dose, and route of opioid use, are summarized in **Table 1**.

Table 1. Sociodemographic and clinical characteristics of the study group

	Mean	SD
Age (years)	27.53	7.1
Duration of illness (years)	7.73	4.8
Heroin dose (grams)	1.30	0.96
	N	%
Gender (Male)	15	100
Marital status		
Unmarried	7	46.7
Married	6	40.0
Divorced	2	13.3
Educational status		
Primary school	10	66.7
High school	4	26.7
University	1	6.6
History of infectious disease	4	26.7
History of substance use treatment	14	93.3
Self-mutilation	1	6.7
Forensic history	9	60.0
Route of heroin use (injecting)	4	26.7
Concurrent use of psychiatric drug	1	6.7

2.3. Data analysis

Descriptive statistics are presented as numbers (side by side with the corresponding percentages), in addition to the mean and standard deviation values. The assumption of normality was checked by using the Shapiro–Wilk test, skewness and kurtosis values, and q-q plot graphs. The Friedman test was used for the analysis of differences between dependent measurements whenever the measurements did not conform to the normal distribution. Dunn's procedure (Bonferroni correction) was used for binary comparisons. P values < 0.05 were considered statistically significant. Statistical analysis was conducted using SPSS 23.0 software.

3. Results

Blood serum NTX levels were measured four times during the study, and at least one of the four measurements was found to be statistically significant (Friedman Chi-squared = 27.088; df = 3; $p < 0.001$). The mean blood serum NTX level was 0.51 ± 1.92 ng/ml at the baseline ('naltrexone0'), 7.88 ± 4.91 ng/ml in the first month ('naltrexone1'), 6.76 ±

Table 2. Changes in biomarkers

	n	Mean±S.D.	Mean Rank	Chi-Square	df	pŧ
ALT (U/L)				1.684	2	0.431
ALT0	15	30.03±26.9	2.27			
ALT1	15	27.60±28.9	1.87			
ALT3	15	22.67±12.2	1.87			
AST (U/L)				6.627	2	0.036*
AST0	15	19.81±4.3	1.57			
AST1	15	22.47±9.3	2.00			
AST3	15	23.00±5.5	2.43			
GGT (U/L)				10,345	2	0.006**
GGT0	15	22.07±16.6	2.33			
GGT1	15	24.47±24.2	2.33			
GGT3	15	17.27±16.1	1.33			
Serum Naltrexone levels (ng/ml)				27.088	3	<0.001***
Naltrexone 0	15	0.51±1.9	1.40			
Naltrexone 1	15	7.88±4.9	3.23			
Naltrexone 2	15	6.76±3.2	3.37			
Naltrexone 3	15	2.75±2.6	2.00			

tFriedman Test, * p<0.05, ** p <0.01, ***p <0.001, df=degrees of freedom
ALT: Alanine aminotransferase
AST: Aspartate aminotransferase
GGT: Gammaglutamyl transferase

3.18 ng/ml in the second ('naltrexone2'), and 2.75 ± 2.59 ng/ml in the third ('naltrexone3'). In binary comparisons, the NTX baseline and the third follow-up blood levels, as well as the first and second NTX follow-up blood levels were found to be statistically equal (p > 0.05 and p > 0.05, respectively; Dunn's procedure (Bonferroni correction)). The blood serum NTX levels were found to be significantly higher at the first follow-up check compared with the baseline, and the same is true of the second check compared with the third (p = 0.001 and p = 0.022, respectively; Dunn's procedure (Bonferroni correction) (**Table 2**; **Figure 1**).

The urine toxicology results of all patients were negative when NTX-XR was initiated; and their urine toxicology follow-ups followed during the first, second, and third months. In these follow-ups, cannabinoid and amphetamine both tested in the first month and amphetamine and ecstasy were both positive in the third month in one patient, while amphetamine and ecstasy were positive in the second month in another patient. All other urine toxicology results were negative.

As to the changes in ALT, AST, and GGT that developed over time after NTX-XR had been administered, mean blood ALT fell within normal limits at the baseline (30.03 ± 26.89), and by the end of the first month (27.60 ± 28.93) and the third (22.67 ± 12.19), and did not change significantly (Friedman Chi-squared = 1.684; df = 2; p = 0.431). AST values too fell within normal limits, but at least one of the three measurements was found to differ significantly from the others (Friedman Chi-squared = 6.627; df = 2; p = 0.036). However, in binary comparisons, no significant differences were found by applying Dunn's procedure (Bonferroni correction). This inconsistency in AST may be due to the fact that the number of subjects in the total sample was insufficient, considering the number of subgroups to be compared. At least one of the three measurements of GGT values was found to differ statistically from the others (Friedman Chi-squared = 10.345; df = 2; p = 0.006). In the binary comparison, the difference between GGT1 and GGT3 was found to be significant with a higher GGT1 (p = 0.019; Dunn's procedure (Bonferroni correction). The difference between GGT0 and GGT3 was found to be significant with a higher measurement at GGT0 (p = 0.019; Dunn's procedure (Bonferroni correction) (**Table 2**).

4. Discussion

The most important result achieved in this stud is that subcutaneous NTX-XR 1000 mg, in week depot form, ensured the desired blood levels, as blood serum NTX levels stayed above 2 ng/ml in the 3 months after administration.

It is known that patients' compliance with treatment with oral NTX is low, so that, in general, with this protocol after a short time the drug is no longer used regularly **[19, 22]**. In one study, free blood serum NTX levels stayed above 2 ng/ml for 145 days following treatment with 3.3 g NTX-XR. In another study it was reported that effective blood levels were

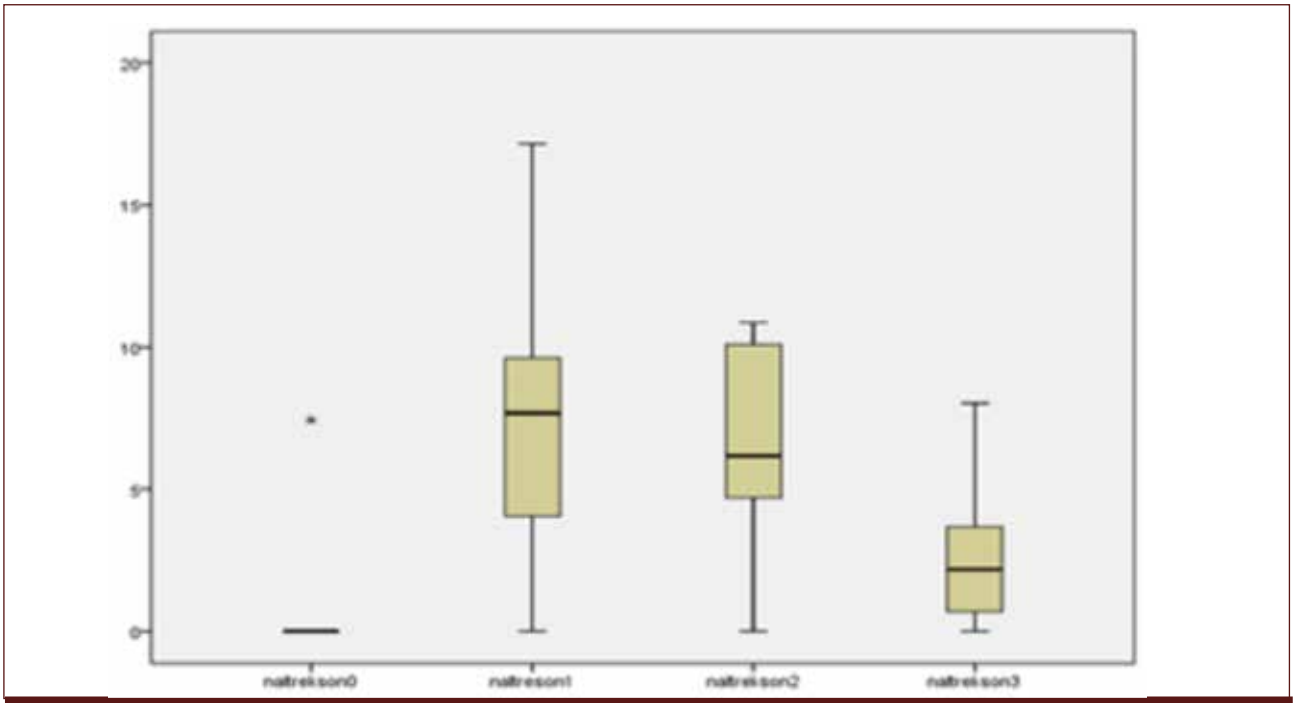

Figure 1. Change in serum naltrexone levels measured at four time points

Naltrexone 0 < Naltrexone 1 (p=0,001)**
Naltrexone 0 < Naltrexone 2 (p<0,001)**
Naltrexone 0 < Naltrexone 3 (p>0,05)**
Naltrexone 1 > Naltrexone 2 (p>0,05)**
Naltrexone 1 > Naltrexone 3 (p=0,053)**
Naltrexone 2 > Naltrexone 3 (p=0,022)**
** **Dunn's** Bonferroni Correction

achieved with 1.1 and 2.2 g NTX-XR treatment for 95 and 136 days, respectively **[17]**. In the present study, blood serum NTX levels remained above 2 ng/ml for 3 months. From this perspective, NTX-XR appears to be a more effective treatment option because it ensures constant blood levels of the drug.

In the present study, when ALT, AST and GGT results were evaluated following NTX-XR treatment, it was observed that there was no significant increase in LFT values with the use of NTX-XR, and similar results have been obtained in studies performed with oral NTX and NTX-XR **[2]**.

NTX-XR treatment has been found to be safe and to reduce opioid use in selected patients **[4, 8-10, 14, 21]**. Similar results were obtained in the present study, and when the results of urine toxicology performed in each of the first three months with 15 OUD patients to whom NTX-XR had been administered, all the opioid test results were found to be negative. This finding suggests a successful outcome in our study group. Likewise, Hulse et al. reported that NTX-XR was more successful than oral NTX in OUD treatment, observing that opioid use tended to resume earlier after oral NTX treatment **[7]**. Increasing the duration of treatment would have the advantage of creating an opportunity for patients to be included in a psychotherapy programme and/or engage in other psychological and social arrangements that would help keep them away from opioids **[5]**.

In a study with 10 patients on 1 g NTX-XR treatment, the time interval required for blood serum NTX levels to fall below 1 ng/ml ranged from 30 to 80 days and the time needed for blood serum NTX level to reach Tmax (i.e. the time required to reach maximum concentration) ranged from 3 hours to 35 days **[18]**. In the present study, even if mean blood serum NTX levels fell significantly between the 60th and 90th days (from 6.76 ± 3.18 to 2.75 ± 2.59 ng/ml; p = 0.022), they were still at an effective blood level. We therefor conclude that this rapid decline after the 60th day should be carefully assessed by clinicians to allow the symptoms of opioid cravings to be properly monitored.

5. Conclusions

Although this is a retrospective study with a small sample size, it is the first study that has been conducted in Turkey to monitor serum levels of NTX after NTX-XR application.

It is our conviction that long-acting depot formulation drugs are more effective than oral NTX, particularly for addicted patients, who have major problems with using medications regularly. The need for regular use is reinforced by the consideration that each day that passes without substance use raises the chances of a patient achieving success through treatment. In conclusion, studies with larger samples on the clinical follow up of NTX-XR with measurement of serum NTX levels may be helpful in guiding policy decisions on how best to conduct future treatments.

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Contributors

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Conflict of interest

All authors declare they have no conflict of interest.

Ethics

Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. The study has received ethics committee approval.

Note

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Somatic diseases in patients with Opioid Use Disorder

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Summary

Background: Compulsive opioid use leading to negative social, occupational, psychological, and physical consequences, including comorbid medical conditions. **Aim:** to assess the somatic diseases found in patients with opioid use disorder over a five-year period. **Methods:** This study has a retrospective cohort design over a five-year period (2013-2017). National patient electronic system "My Term" was used to collect data. The variables: gender, age, ethnicity, employment, duration and route of opioid administration, duration of hospitalization, somatic diseases, types of opioid substances used were analysed. **Results:** In all, 142 patients with opioid use disorder were analysed. The male gender was predominant. The mean age of patients in this study was 36.12±5.39, with average duration of opioid use disorder of 10.58±3.50 years. In the three groups of patients selected (current injectors, former injectors and oral users), methadone was the most frequently used drug (61.27%), followed by heroin (28.87%). Benzodiazepines were the second most frequently used drug (5.63%), mainly among current injectors (6.73%). About 33.10% of the patients had more than one somatic disease. **Conclusions:** Methadone was most commonly used as a single or combined substance in patients with opioid use disorder. Benzodiazepines were the second most frequently used drug, mainly among current injectors. The most frequent medical problems among current and former injectors were vascular changes, followed by skin changes and infections. Respiratory medical problems were common among patients with opioid use disorder who used drugs via inhalation.

Key Words: Opioid Use Disorder; opioid substance; somatic diseases; early diagnosis

1. Introduction

By now it has become clear that opioids have important effects on many physiological and pathological processes that undoubtedly have an impact on the immune, respiratory, brain and cardiovascular systems **[1, 7, 16, 19, 20, 23]**.

Heroin use is associated with numerous adverse sequelae. The parenteral use of opioid drugs is a central factor, and other risk factors include polydrug use, particularly of benzodiazepines and alcohol **[13, 15]**, mental health issues **[14, 25]** and environmental factors not conducive to better health. Medical complications of heroin affect a number of different organ systems. The role of the addiction specialist is to be aware of these, so that early diagnosis and appropriate management are made possible. Good management will usually depend on effective collaboration with other specialists. The addiction specialist can play a significant role in the development of clinical systems to ensure that these complications are minimized **[24]**.

No matter how they ingest the drug, chronic heroin users experience a variety of medical complications. Lung complications (including various types of pneumonia and tuberculosis) may result from the poor health of the user, as well as from heroin's effect of impairing respiration. Many of these patients experience mental disorders, such as depression and antisocial personality disorder. Men often experience sexual dysfunction, while women's menstrual cycles often become irregular. There are also specific consequences associated with different routes of administration. For example, people who repeatedly snort

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heroin may damage the mucosal tissues in their noses, besides perforating the nasal septum. Medical consequences of chronic injection use include scarred and/or collapsed veins, bacterial infections of the blood vessels and heart valves, abscesses (boils), and other soft-tissue infections. Many of the additives in street heroin include substances that do not readily dissolve and clog the blood vessels that lead to the lungs, liver, brain or kidneys. This can cause infection or even the apoptosis of small cell areas in vital organs. Immune reactions to these or other contaminants can cause arthritis or other rheumatological problems. Sharing of injection equipment or fluids can lead to some of the most severe consequences of heroin use: infections with hepatitis B and C, HIV, and a host of other blood-borne viruses, which drug users may then pass on to their sexual partners and children **[17]**.

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) gives 11 criteria for opioid use disorder (OUD), two or more of which must be met for a diagnosis of OUD. These criteria emphasize continuous and compulsive opioid use leading to negative social, occupational, psychological, and physical consequences, including comorbid medical conditions **[21]**.

The widespread use of heroin has revealed the increasingly life-threatening complications consequent on drug-taking. The effects of heroin on the cardiovascular, pulmonary, renal and central nervous systems have been well described in the medical literature, but the vascular complication of chronic occlusive arterial disease of the lower limbs is a rare event **[4]**.

Aim: The aim of this study has been to assess the somatic diseases in patients with opioid use disorder over a five-year period.

2. Methods

2.1. Design of the study

The Skopje University Clinic of Toxicology is part of the largest national tertiary care centre, situated in the "Mother Teresa" campus in Skopje, Republic of North Macedonia. The main aim of this Clinic is to function as an emergency centre for internal diseases; the clinic has the same location as toxicology department.

This study has a retrospective cohort design, lasting over a five-year period (2013-2017). It included a total of 142 patients, each of whom had been given a diagnosis of OUD, according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). The participants were recruited through their treatment contacts. Patients were examined and treated according to the precise nature of their somatic diseases. This called for close collaboration between the leading specialists and various subspecialists, while taking care throughout the treatment of these patients' underlying disease, OUD. This institution is visited by these patients for one of the following reasons: overdoses with illicit and/or prescribed drugs, clinical examination and the treatment of somatic diseases despite ongoing opioid use, detoxification, or withdrawal symptoms, or else the initiation of treatment for OUD, with buprenorphine employed as a replacement for opioids. All participants were interviewed and a complete clinical examination was performed by the specialists in internal medicine at the University Clinic of Toxicology.

2.2. Sample

Twenty-five patients refused to undergo the planned clinical investigations and medical treatment. The patients who decided against participating had socioeconomic, demographic and clinical features comparable with those who participated in this study. The following inclusion criteria were applied: a current diagnosis of OUD, according to the criteria set out in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), a positive toxicological screening result for opioids, the presence of somatic disease. A somatic disease incident was defined as any acute or subacute health problem that led to inpatient or outpatient hospital treatment. Exclusion criteria were as follows: patients with OUD but without somatic disease, and patients without confirmation of a diagnosis of OUD.

2.3. Data

The national patient electronic system "My Term" was used to collect data. The variables: gender, age, ethnicity, employment, duration and route of opioid administration, duration of hospitalization, somatic diseases, kinds of opioid substances used were all analysed. Each patient was interviewed and underwent clinical and psychiatric examinations. The images collected were approved in advance through the written consent of the patients.

2.4. Data analysis

Data were statistically analysed by using the SPSS software package, version 22.0 for Windows (SPSS, Chicago, IL, USA). The qualitative series were processed by determining the coefficient of relations, proportions and rates, and were shown as absolute and relative numbers. Quantitative series were analysed by taking measures of central tendency (average, median), as well as by taking dispersion measures (standard deviation, standard error). Pearson Chi-squared test, Yates corrected, Fischer exact test, and Fisher-

Feeman-Halton exact test were used to determine the association between certain attributive dichotomies. Difference test was used to compare proportions. A two-sided analysis with a threshold level of $p<0.05$ was used to determine statistical significance.

3. Results

During the study's five-year duration, a total of 142 patients with OUD were analysed. The most dominant were current injectors – 104 (73.2%) – followed by former injectors – 20 (14.1%). There was no significant association between the route of drug administration and gender (Fisher-Feeman-Halton exact test: p=0.3188). We found no significant age-related differences between patients who were using different routes of drug administration (Kruskal-Wallis H test: Chi-squared (4)=3.988; p=0.4076). Comparison of proportions of current as well as previous drug injectors, first between Macedonians and Albanians, and then between Macedonians and others, did not differ significantly, yielding the following data: (Difference test: 13.3% (95% CI (-8.06-27.44)); p=0.2027) vs. (Difference test: 14.02% (95% CI (-9.96-28.47)]; p=0.2271) and (Difference test: 8.13% (95% CI (-10.95-18.68)); p=0.3306) vs. (Difference test: 11.27% (95% CI (-9.82-20.90)); p=0.2209). Current and previous injectors had a significantly lower employment rate than patients who practised other routes of drug administration (Fisher-Feeman-Halton exact test: p=0.048) (**Table 1).**

The analysis showed no significant association between the route of drug administration and number of substances used (Fisher-Feeman-Halton exact test: p=0.254). In three groups of patients (current injectors, former injectors and oral users) the most commonly used drug was methadone (61.27%) followed by heroin (28.87%). Benzodiazepines were the second most frequently used drug n=53 (94.64%) mainly among current injectors n=42 (97.67%). Among both current and previous injectors, the most frequent combination was methadone and benzodiazepines. Among current injectors with benzodiazepines, 5 patients were on opioid agonist treatment with methadone, while 2 others were in opioid agonist treatment with buprenorphine. The only patient who reported the current injection of amphetamines was in buprenorphine maintenance. The most frequent medical problem both among current and previous injectors was vascular changes (67.31% vs. 70.00%), followed by skin problems (20.19% vs. 25%) and infections (17.31% vs. 25%) (**Figure 1).**

Respiratory medical problems were dominant among patients with OUD who used drugs via the inhalation (60%) or sublingual route (66.7%). Forty-seven (33.10%) patients had two somatic diseases, with a significant linear positive weak correlation between the duration of opioid use and the the number of medical problems experienced (Spearman Rank Order correlation: R=0.202; p=0.016). Only 49 patients were tested for hepatitis B, C and HIV infection. Anti-HCV positivity was detected in 65.28% and HBsAg positivity in 2.78% of all the patients examined. None of the patients had an HIV infection. No significant association was found between in/out medical treatment and the route of drug administration (Fisher-Feeman-Halton exact test: p=0.174). Duration of hospitalization was not found to differ significantly between patients using different routes of drug administration (Kruskal-Wallis H test: Chi-squared (4)=3.496; p=0.4785). Eleven (7.7%) hospitalized patients had to be transferred to another department. Medical treatment was halted by 9 (5.3%) patients with OUD, but no association was found in these cases with the route of drug administration (Fisher-Feeman-Halton exact test: p=0.106). During the period of the study 4 patients died; of these, 2 (50%) had respiratory problems, 1 (25%) had diabetes and 1 (25%) malignancy (**Table 2** and **Figure 2**)

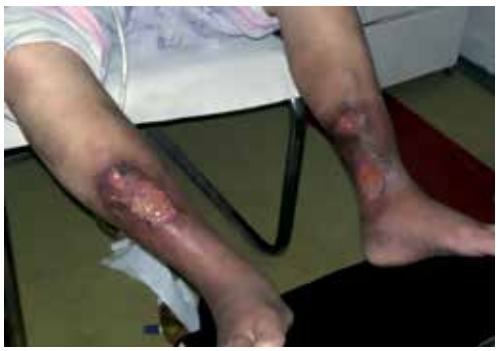

Figure 1. Female, 35 years old with 11 years with opioid use disorder on AOT with methadone (former injector)

4. Discussion

Besides psychiatric comorbidity among patients with opioid use disorder (OUD), in this population there is always a risk of contracting other infectious and non-infectious conditions. The main aim of this study was to show the most frequent somatic diseases in patients with OUD treated at the University Clinic of Toxicology in Skopje during a five-year period. In all, 142 patients with OUD were examined in this study. Male gender was predominant (89.44%). The mean age of patients in this study was 36.12±5.39, with the average duration of OUD at 10.58±3.50 years. Concerning the routes of administration in our study, the most frequent choice was that made by current injectors (73.24%).

Table 1. Demographic characteristics of patients with Opioid Use Disorder (2013-2017)

	Current injectors		Former injectors		Inhalation		Oral		Sublingual		Total	
Parameter	N	%	N	%	N	%	N	%	N	%	N	%
Years of treatment												
2013	26	81.25	6	18.75	-	-	1	3.03	-	-	33	23.24
2014	25	67.57	6	16.22	2	5.41	3	8.11	1	2.70	37	26.06
2015	22	73.33	2	6.67	-	-	4	13.33	2	6.67	30	21.13
2016	16	72.73	3	13.64	2	9.09	1	4.55	-	-	22	15.49
2017	15	75.00	3	15.00	1	5.00	1	5.00	-	-	20	14.08
Total	104	73.24	20	14.08	5	3.52	10	7.04	3	2.11	142	100
Gender												
Male	96	92.31	17	85.00	4	80.00	8	80.00	2	66.67	127	89.44
Female	8	7.69	3	15.00	1	20.00	2	20.00	1	33.33	15	10.56
Ethnicity												
Macedonia	70	67.31	17	85.00	4	80.00	8	80.00	2	66.67	101	71.13
Albanian	19	18.27	2	10.00	1	20.00	-	-	1	33.33	23	16.20
Other	15	14.42	1	5.00	-		2	20.00	-	-	18	12.67
Employment, past month												
Not employed	95	91.35	19	95.0	3	60.0	7	70.00	3	100	127	89.44
Employed	9	8.65	1	5.00	2	40.0	3	30.00	-	-	15	10.56
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	36.15	5.34	37.05	5.17	31.40	6.23	35.77	6.30	37.67	1.53	36.12	5.39

Common OUD-associated medical conditions may result from behaviours (e.g., drug use by injection) related to opioid use or from the direct pharmacological effects of opioids. This distinction is important because it highlights the fact that much of the harm done by illicit opioid use comes from unsafe injection practices **[17]**. Adulterants that dilute the effects of opioids, such as caffeine, quinine, and sugar, may have health consequences when injected **[6]**. Syringes, cookers, water, and filters used in preparing opioids for injection also may function as a channel for infectious disease transmission, particularly when they are shared or reused, or if non-sterile **[22]**. Likewise, injecting crushed prescription opioids may lead to adverse skin reactions and limb ischaemia due to talc or other inactive ingredients put into tablets **[21]**. In our study 27 patients had skin changes: 16 patients had ulcers on the lower limbs (six of them also had varicose veins, three of them developed gangrene and finished their treatment with amputation), 7 patients had ulcers on the upper limbs, and 4 showed areas of hyperpigmentation on the lower limbs. People who inject drugs may prefer injecting into a vein ('mainlining'), muscle ('muscling'), or subcutaneous or intradermal tissue ('skin-popping'). Each site of injection carries different risks **[3]**. In our study one patient had acquired the habit of intraperitoneal injection of methadone. He developed peritonitis. Parenteral injection may introduce bacteria beneath the skin and into the bloodstream from contaminated injection supplies, non-sterile water, or unsterilized skin **[8, 21]**. Our study showed that, of the total number of patients examined, (16.20%) had a variety of infections, as follows: 3 patients had sepsis, 5 had erysipelas on the lower limbs, 2 developed infective endocarditis, 6 had an abscess, and 7 were affected by cellulitis. Skin and soft tissue infections (SSTIs) are the most common reason for hospital admission among people who inject drugs **[5, 21]**. The spectrum of SSTIs and their sequelae includes abscesses, cellulitis, systemic sepsis, necrotizing fasciitis, pyomyositis (abscesses of skeletal muscle), abscesses affecting visceral organs, bone/joint infections, and endovascular infections. Among those who inject drugs, abscesses are the most common kind of SSTIs, presenting as red, tender fluctuant areas on the skin **[12]**. Most SSTIs are caused by commensal flora, but contaminated drugs, drug adulterants or drug use paraphernalia may function as alternative ways of introducing bacteria **[8]**. Within five years of injection drug use (IDU) initiation, more than one in five people become infected with HCV. In our study, 49 patients were tested, and anti-HCV positivity was detected in 65.28% of them. Endovascular infections, including infective endocarditis, septic thrombophlebitis, and mycotic aneurysms create risks of IDU **[21]**. In our study the most frequent medical problem among current and previous injectors were vascular changes (59.15%). Of the

Table 2. Substance use and medical condition characteristics of patients with opioid use disorder (2013-2017)

	Current injectors		Former injectors		Inhalation		Oral		Sublingual		Total	
Parameter	N	%	N	%	N	%	N	%	N	%	N	%
Number of used substance												
One	61	58.65	11	55.00	4	80.00	7	70.00	3	100	86	60.56
Two	43	41.35	9	45.00	1	20.00	3	30.00	-	-	56	39.44
Type of drug												
Heroin	30	28.85	5	25.00	5	100	1	10.00	-	-	41	28.87
Methadone	65	62.50	14	70.00	-	-	8	80.00	-	-	87	61.27
Benzodiazepines	7	6.73	-	-	-	-	1	10.00	-	-	8	5.63
Amphetamine	1	0.96	-	-	-	-	-	-	-	-	1	0.70
Buprenorphine	1	0.96	1	5.00	-	-	-	-	3	100	5	3.52
Medical problems												
Vascular changes	70	67.31	14	70.00	-	-	-	-	-	-	84	
Infection	18	17.31	5	25.00	-	-	-	-	-	-	23	
Cardiovascular	1	0.96	-	-	1	20.00	3	30.00	-	-	5	
Respiratory	8	7.69	1	5.00	3	60.00	3	30.00	2	66.67	17	
Neurological	4	3.85	-	-	-	-	-	-	-	-	4	
Gastrointestinal	6	5.77	2	10.00	1	20.00	2	20.00	-	-	11	
Rhabdomyolysis	6	5.77	-	-	-	-	-	-	-	-	6	
Acute renal failure	4	12.50	-	-	-	-	-	-	-	-	4	
Skin changes	21	20.19	5	25.00	-	-	1	10.00	-	-	27	
Diabetes	-	-	-	-	-	-	1	10.00	-	-	1	
Hematologic	-	-	-	-	-	-	2	20.00	-	-	2	
Malignancy	-	-	-	-	-	-	1	10.00	1	33.33	2	
Hepatitis												
Anti-HCV pos.	32	68.09	8	17.02	1	2.13	3	6.38	3	6.38	47	65.28
HbsAg pos.	2	100	-	-	-	-	-	-	-	-	2	2.78
Treatment												
Inpatients	52	50.00	11	55.00	3	60.00	2	20.00	-	-	68	47.89
Outpatients	52	50.00	9	45.00	2	40.00	8	80.00	3	100	74	52.11
Treatment interrupted	5	4.81	1	5.00	-	-	3	30.00	-	-	9	5.34
Agonist Opioid Treatment												
Methadone	50	48.08	12	60.00	-	-	8	80.00	-	-	70	49.30
Buprenorphine	13	12.50	1	5.00	-	-	-	-	3	100	17	11.97
Heroin-black*	29	27.88	5	25.00	5	100	1	10.00	-	-	40	28.17
Methadone-black*	12	11.54	2	10.00	-	-	1	10.00	-	-	15	10.56
Exitus	1	0.96	-	-	-	-	2	20.00	1	33.33	4	2.82%
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Duration of hospitalization (days)	12.65	5.97	12.33	6.56	10.50	2.12	8.62	7.01	14.67	12.66	10.58	3-50
Duration of opioid use (years)	10.65	3.44	11.00	3.52	7.40	2.70	11.20	4.37	8.67	1.53	10.58	3.50

*black market

total number of patients, 11 had deep vein thrombosis in the upper limbs, 68 showed deep vein thrombosis in the lower limbs (4 of these patients subsequently developed pulmonary thromboembolism), one patient had thrombosis of the inferior vena cava, and 4 had femoral vein aneurysm. After drug injection, 4 patients developed neurological disorders (nerve paresis). A total of 21 patients came to our clinic as a result of overdose with methadone and 11 with heroin. After that 6 of them developed only rhabdomyolysis, while 4 others developed rhabdomyolysis leading to acute renal failure. Rhabdomyolysis after intravenous

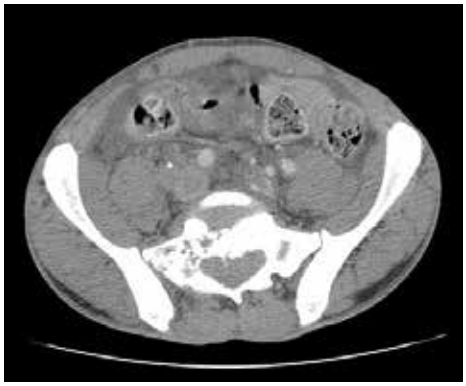

Figure 2. Male, 31 years old, with 9 years opioid use disorder on opioid agonist treatment with Buprenorphine (lethal outcome)
CT (computer tomography) of the abdomen; postcontrast series; venous phase; section at height of the entrance to the small pelvis. Clear display of the iliac veins (arrow); the right vein is with wider lumen and with visible intraluminal thrombotic masses. Right lateral mass of sacrum is structurally modified with osteolytic changes and soft tissue substrate (black arrow). Soft tissue substrate is in the spinal canal.

heroin abuse has been reported in heroin-addicted patients [9].

Another common mode of opioid administration is intranasal insufflation (sniffing) of powdered or dissolved opioids. Intranasal insufflation can lead to other comorbid conditions, including asthma exacerbation, sinus problems, hypersensitivity pneumonitis, nasal septum necrosis or perforation [18]. In our study 5 patients administered heroin by intranasal insufflation. Two patients had pneumothorax, two patients had pulmonary infection and asthma exacerbation, and one patient had tuberculosis. Pulmonary infections, including pneumonia, tuberculosis (TB), and septic emboli are other common complications of IDU. In patients who present with cough, shortness of breath, and increased sputum production, a chest x-ray may appear normal, so making diagnosis much more difficult [10].

Many people with OUD have other substance use disorders that can lead to significant medical complications. Polysubstance use is associated with substantial morbidity and mortality. Benzodiazepine use disorder is common among people with OUD and dramatically increases overdose risk [11]. In our study, considering the whole group of current injectors, as many as 41.35% used a combination of two psychotropic substances. The most commonly used combination was methadone and benzodiazepines.

In our study 5 patients were affected by cardiovascular disorders. Three of them had cardiac arrhythmia, and two of them had acute coronary syndrome. The cardiac arrhythmogenicity produced by various opioids is a different matter. Methadone in conventional doses has a higher capability to induce long QT intervals and dangerous arrhythmias than other forms of therapy [2]. One study showed that coronary artery disease (CAD) in patients with drug use was significantly higher than in the group without any drug use [2]. In our study there were 11 patients who had gastrointestinal disorders. As already mentioned, one patient had peritonitis; 3 patients had pancreatitis, 5 patients showed the presence of cirrhosis (of these, four were hepatitis C positive, and the fifth was HBsAg positive), 2 patients had gastrointestinal ulcers. Two patients had haematological disorders: one patient had Non-Hodgkin's lymphoma, and the other had polyclonal gammopathy. Our study also included 2 patients with malignant diseases. One patient was affected by a metastatic process on the skeletal muscles, and he had a lethal outcome; the other one had a malignant melanoma.

Implications for practice

Healthcare professionals should be aware that patients with OUD are not individuals who suffer only from mental disorders. This population is at risk for infectious and non-infectious conditions alike. Prevention, rapid diagnosis and appropriate treatment are needed to protect this population, along with the rest of the population.

Limitations

The following limitations should be considered when interpreting our findings. The study included only outpatients who came to our clinic; as a result, the generalizability of the results may be limited. Not all of our patients were screened serologically for hepatitis B, C and HIV". Further research is needed on the most frequent somatic diseases among patients with OUD, when compared with other individuals. Further studies are needed on the frequency of somatic diseases among patients who are on opioid agonist treatment with buprenorphine in comparison with those who are on opioid agonist treatment with methadone.

5. Conclusions

Methadone has been most commonly used as a single or combined substance in patients with opioid use disorder. Benzodiazepines were the second most frequently used drug, mainly among current injectors. The most frequent medical problems among current and former injectors were vascular changes, followed by skin changes and infections. Respiratory medical

problems were dominant among patients with opioid use disorder who were taking drugs via inhalation.

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Contributors

N.S, initiated the study, contributed to the study conception and design. A.B, Z.P, K.K, K.N obtained data. V.V.S reviewed the study parameters and contributed to the analysis plan, statistical analysis and interpretation of the results. All authors revised and approved the final manuscript.

Conflict of interest

The authors have no conflict of interest.

Ethics

Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects.

Note

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Patterns of pain killers and other opioid use in patients admitted to a detoxification and Dual Diagnosis Unit, 2016-2019: A retrospective cohort study

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Summary

Background: Increasing opioid consumption in recent years has given rise to compelling significant concerns. Fentanyl, heroin, new psychoactive substances and prescribed opioids have been named as the main substances involved in the 'opioid epidemic'. **Aim**: To analyse the pattern of opioid use in the Detoxification and Dual Disorders Unit of Salamanca (Spain) across 2016 to 2019. **Methods**: Data were collected retrospectively from a sample of 795 patients (611 men and 184 women) admitted to the Detoxification and Dual Diagnosis Unit from 2016 to 2019, inclusive. **Results**: 350 (44%) of all patients admitted were diagnosed with an opioid-related disorder. Around two-thirds (N=232) of these had a pattern of polydrug misuse. The relatively small number of patients with opioid dependence due to prescribed painkiller dependence increased from 1% to 5% during the study period. Cancer was the commonest indication for prescribed opioids. Patients with dependence on prescribed opioids tended to be older than those with other patterns of use (47.9 years old compared with 44.0 years) and women were over-represented in this group (9% of opioid dependence in women compared with only 1% in men), and those patients had high levels of anxiety and depression diagnoses. **Conclusions**: Knowing about this situation provides a better perspective for working on treatment plans. We need clear interventions and management strategies to detect the misuse or abuse of painkillers.

Key Words: Opioid crisis; dual disorder; pain killers; drug dependence; detoxification; heroin; polydrug use

1. Introduction

The use of opioids, whether legal or illegal, has risen in recent years. It is a major public health problem, sometimes described as an "epidemic" , with more than 64,000 deaths in 2016 in the US **[21]** and 6,581 – as many as 85% of drug-induced deaths – in Europe **[9]**. Different factors have been suggested for this increase in opioid consumption. Fentanyl, heroin, new psychoactive substances (NPS) and prescribed opioids have been named as the main substances involved in the "opioid epidemic" (**Figure 1**) **[1, 6, 8, 9, 11, 21]**.

On the EU drug market heroin is the most commonly traded opioid **[8]**. It is responsible for a large share of the harm done to individuals that is related to drug use in the EU, in particular, drug-related deaths **[9]**. In addition, fentanyl-contaminated heroin

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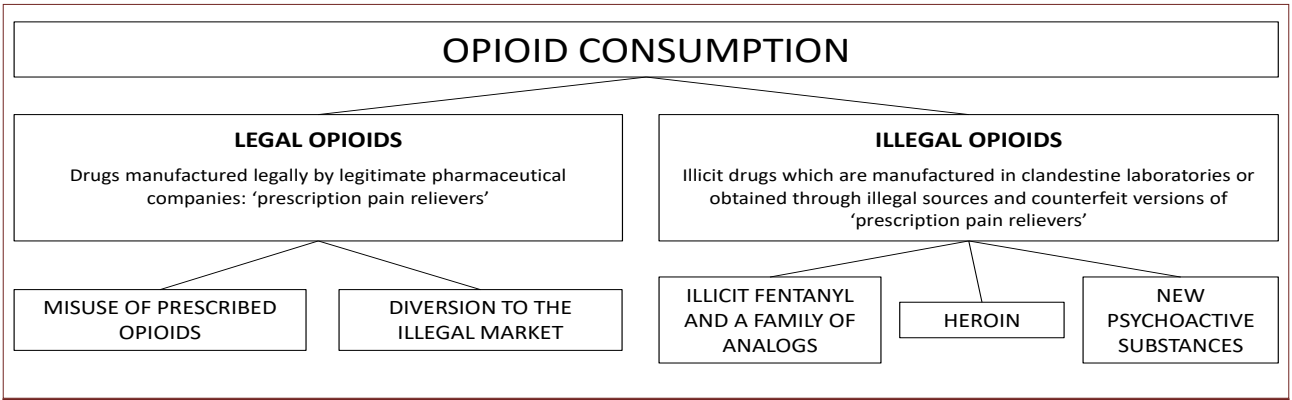


Figure 1. Substances contributing to the opioid crisis

fentanyl (FCH) is becoming commoner and needs to be combated, as associated morbidity and mortality have adversely impacted American healthcare systems [14].

Although heroin is the best known of all the illicit opioids, fentanyl has been suggested as one of the foremost agents responsible for opioid epidemics [3, 13, 21]. On the one hand, prescribed fentanyl can be misused or diverted to the street market. On the other, illicit fentanyl is used in counterfeit prescription drugs and may be cut into heroin or other drugs as an additive or adulterant [21]. Its high potency, low cost and easy manufacturing are characteristics that make it an attractive commodity for drug dealers and abusers [2]. However, fentanyl use carries higher risks, especially the risk of death due to overdose (intravenous administration may cause rapid and deep respiratory depression within minutes).

Another increasingly important cause of concern is widespread recourse to non-controlled synthetic opioids. European agencies actively monitor 731 NPS [9, 38]. Despite the work of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in monitoring these drugs to reduce the severe damage they cause, around 50 new substances are reported to the EU Early Warning System annually [7]. Even when a novel product is given fast track status for review, it can take months or years for it to become recognized as a scheduled controlled substance because the authorities have to accumulate a substantial amount of data about its use, abuse and associated morbidity/mortality [37]. In addition, the NPS market is distinguished by rapid product entry and exit. Moreover, many NPS products arrive at specialty shops and can be sold with few or no legal restraints in communities where the authorities may be unaware of their availability [30].

Lastly, as already pointed out in discussing fentanyl, prescribed opioids have become a major feature of what has become known as the 'opioid crisis'. An increase in the regular prescription of opioids has been reported in the last few years. According to the study by Mazer-Amirshashi et al., opioid prescriptions in hospital emergency departments continued to increase while the prescription of non-opioid analgesics remained unchanged in the same time period [17]. This more easygoing prescription of opioid analgesics may have been initiated a quarter of a century ago, when the World Health Organization (WHO) strongly advocated pain control; since then, being free of pain has been considered a fundamental human right [34]. Even so, it may be argued that the countless prescriptions of opioid analgesics are not based on genuine scientific principles or any true medical need. They are, rather, rooted in traditions, expert opinion, anecdotal evidence, vigorous marketing by pharmaceutical companies, and the loosening of laws and restrictions on opioid use [15]. However, the misuse of prescribed opioids by their owners plays a relatively minor role in the opioid crisis, since many of these prescribed opioids find their way into the hands of recreational abusers; those doses often reach their consumers after being bought, stolen or borrowed from family members or friends [31], (**Figure 1**). In some countries, there have been reports of abusers of painkillers who later switch illegal opioids. This would probably be less likely in Spain, because of the universal access to public health services [25]. In any case, apart from heroin, other opioids available on illicit markets in Europe include opium and the medicines morphine, methadone, buprenorphine, tramadol and various fentanyl derivatives [8].

In summary, there have been profound changes in opioid consumption in recent years, and these can only be expected to continue. The opioid market is becoming more diverse and complex, with high-potency synthetic opioids, in particular, posing considerable challenges [9]. In this context, having deeper knowledge about the situation in our environment could give us a better perspective from which to work out prevention and treatment plans.

Table 1. Age and sex distribution of the whole sample (N=795)

		2016	2017	2018	2019	Overall
Age	Mean (SD)	43.3 (8.8)	44.0 (9.7)	43.5 (9.7)	45.3 (9.6)	44
Age range	min-max	19-67	19-71	19-66	18-65	18-71
Gender	Male (n/%)	167 (78.8)	155 (75.6)	152 (77.9)	137 (74.9)	611 (76.9)
	Female (n/%	45 (21.2)	50 (24.4)	43 (22.1)	46 (25.1)	184 (23.1)

Aim: To analyse patterns of opioid use in patients admitted to the Detoxification and Dual Disorders Unit of Salamanca (Spain) from 2016 to 2019, inclusive.

2. Methods

In this study, retrospective data were collected from a sample of 795 patients (comprising 611 men and 184 women) admitted to the Detoxification and Dual Diagnosis Unit of Salamanca, Spain, from January 1, 2016 to December 31, 2019. We recorded: (1) Demographic data; (2) Distribution of patients according to the kind of substance used; the percentage of patients treated for the use of opiates with respect to other drugs is described here, as well as patterns of opioid use in our sample; and (3) Characteristics of the prescribed opioid users in the sample.

3. Results

3.1. Demographic data

The age and sex distribution of the whole sample of 795 patients is shown in **Table 1**. Males outnumbered females in each year and the mean age remained similar throughout the study period.

3.2. Patterns of substance dependence in the four-year period 2016-19

The mean proportion of patients with opioid dependence was 44% across the 4-year period 2016-19, with little variation and no evidence of any rising or falling trend (**Figure 2**).

Among patients with opioid dependence, the most common pattern of consumption was polydrug use, defined as a combination of an opioid (generally heroin or methadone) with a variety of other drugs (alcohol, benzodiazepines, cocaine, cannabis, amphetamines, hallucinogens, or others). Overall, polydrug use was seen among 232/350 (66.3%) of patients admitted with an F11 diagnosis (**Figure 3**).

Over the study period, the percentage of cases with polydrug use increased from 57% to 84% among cases of opioid-related disorders. The most frequently used combinations of drugs were heroin and/or methadone with alcohol, cocaine or benzodiazepines. This increase in polydrug dependence corresponded to a fall in dependence on methadone alone in 2018 and 2019.

Over the 4-year period, there were small increases in (a) patients treated for heroin dependence (from 3% in 2016-17 to 8-14% in 2018-19 among cases of opioid-related dependence) and (b) patients treated for the use of painkillers (from 1-2% in 2016-17 to 4-5% in 2018-19 among cases of opioid-related dependence) (**Figure 3**).

There were more men than women in every category of opioid use (**Figure 4**). However, the proportions of women with polydrug dependence and/or dependence on painkillers were higher than for men. On the other hand, the proportion of males admitted because dependent solely on heroin, methadone or buprenorphine was higher than for females.

3.3. Dependence on painkillers and prescribed opioids

Although the numbers of patients with dependence on painkillers were small, we were particularly interested in this group because of recent concerns about the issue in the literature (as described in our introduction). Altogether, there were 12 patients with painkiller dependence in our sample, amounting to just 3.5% of patients with opioid dependence. It must, however, be considered that the four women with painkiller dependence were 9% of the number of women admitted. Furthermore, the numbers of patients admitted rose over the 4-year study period, which strongly suggests that the problem is growing. The age distribution in this group was noteworthy, with a slightly higher mean age than the general sample (47.9 years: 46.5 for women and 48.6 for men), a higher minimum age (35 years), and a higher mean age at onset of consumption (40.8 years: 41.5 for women and 40.4 for men).

All the patients in this group misused opioids, which had been prescribed for a variety of diagnoses, including cancer, fibromyalgia, trauma and chronic pancreatitis (**Figure 5**). The types of cancer included multiple myeloma, lymphoma, oropharyngeal cancer and unspecified cancer. Four of the patients, all men, also showed dependence on other drugs as well as

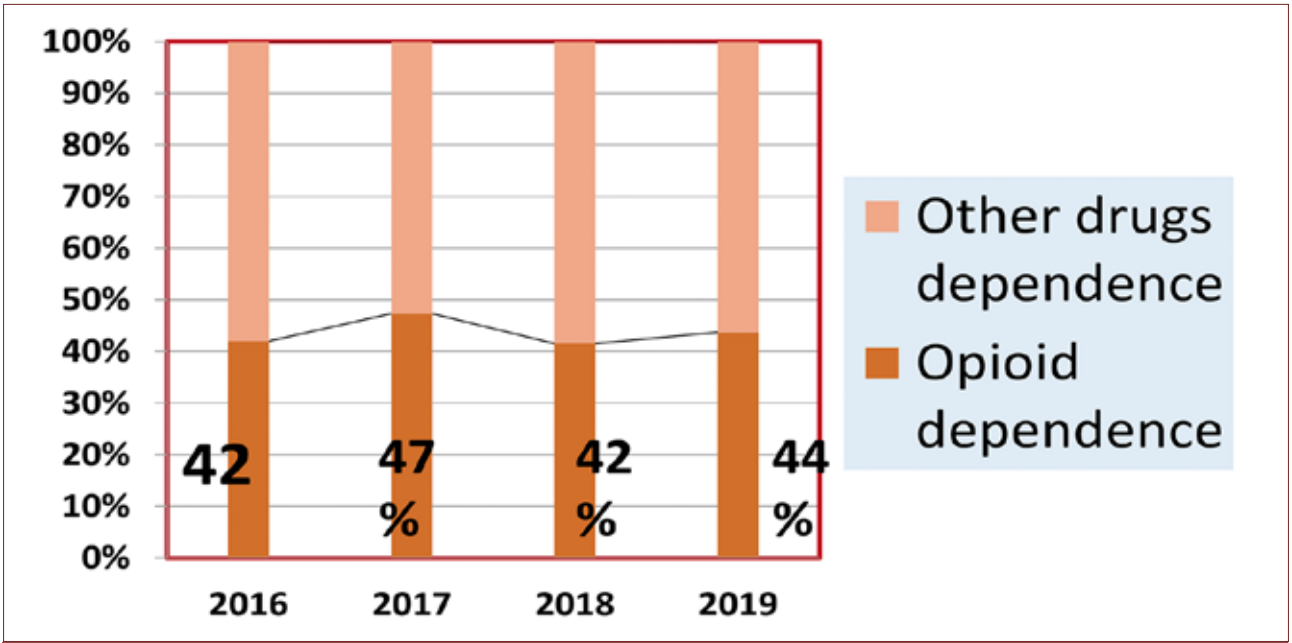


Figure 2. Opioid dependence among patients admitted to the dual diagnosis unit of Salamanca with respect to dependence of other drugs in a 4-year period (2016-2019).

prescribed opioids: anxiolytics (N=2), cocaine (N=1) and alcohol (N=1). Patients with painkiller dependence had a high level of psychiatric comorbidity. Ten of the 12 patients (85%) had another psychiatric diagnosis, including anxiety disorder (N=4), depression (N=3), and personality disorder (N=3).

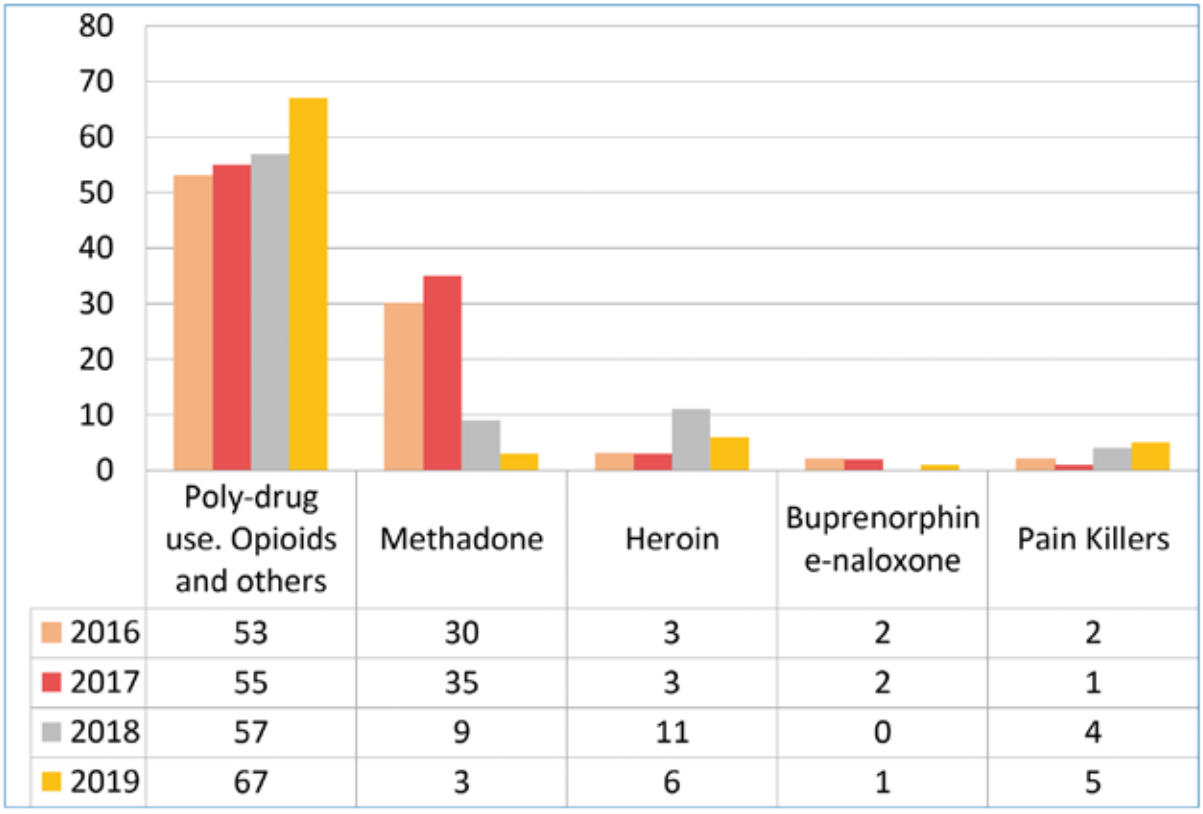
4. Discussion

Our main findings are that almost the half of this sample of patients admitted to a dual diagnosis unit had an opioid-related disorder, and that by far the commonest pattern of dependence was polydrug use. High-risk opioid use causes most of the health and social burdens associated with drug use **[28]**. Besides the risks inherent in consumption, individuals with opioid use disorder may face discrimination, unfair treatment and difficulty in accessing healthcare services **[12, 18, 26, 35]**. The combination of these factors is associated with poor outcomes for these patients **[4, 5, 10, 20, 36]**.

Heroin is the most commonly used opioid in most countries in Europe, with some exceptions, e.g. fentanyl and buprenorphine in Estonia and Finland, respectively **[28]**. In keeping with this and other studies **[2, 3, 13, 14, 21, 22]**, we have observed an increase in patients treated for heroin dependence in the last four years.

Furthermore, non-controlled synthetic opioids are a growing cause for concern, with a rapid increase seen in the number of fentanyl derivatives, substances particularly associated with fatal poisoning. Carfentanil, for example, is one of the most potent opioids known; it is used as a veterinary medicine for the immobilization of large animals, and is very lethal in overdose **[9]**. More than 40 deaths were reported to the EMCDDA within months of the detection of the opioids AH-7921 and MT-45 on the European drug market **[6]**. However, our sample did not include any data about the use of illicit fentanyl or other analogues, as described in the literature **[21]**. Instead, in our sample, all patients treated for any painkiller dependence had received a prescription for opioid treatment as an analgesic for a documented medical diagnosis, most commonly cancer. It is, however, possible that the use of fentanyl derivatives has been under-reported in our data.

In connection with the issue of psychiatric comorbidity among painkiller-related disorders, it may be observed that comorbidity is very prevalent in the study, with as many as 85% of this group showing a dual disorder. Anxiety disorder proved to be the most prevalent in the sample (30%), closely followed by depression (25%). These results make perfect sense, since depression and anxiety have been associated with increased perception of pain severity, besides which the prolonged duration of acute pain leads to increased mood dysregulation **[19]**. It should be borne in mind that psychopathology has been a predisposing factor or a consequence of opiate dependence in these patients **[29]**. A review of public databases found that dual diagnosis is very prevalent among psychiatric patients, and that patients in methadone maintenance treatment displayed multiple psychiatric or medical conditions – a finding that, in its turn, translates into a failure in compliance with treatment **[23]**. In our sample, psychiatric comorbidities were more prevalent in males (88%) than females (75%). This finding



	Poly-drug use. Opioids and others	Methadone	Heroin	Buprenorphine-naloxone	Pain Killers
2016	53	30	3	2	2
2017	55	35	3	2	1
2018	57	9	11	0	4
2019	67	3	6	1	5

Figure 3. Opioid dependence according to the type of opioid, in a 4-year period (2016-2019).

contrasts with the preceding data, where it is said that women with OUD are more likely to experience psychological and physical symptoms [32]. In any case, this discrepancy calls for cautious interpretation, since males outnumber females in our sample.

The commonest pattern of drug use in our sample was polydrug dependence, and the proportion rose over a 4-year period. By 2019, 84% of patients with opioid dependence were polydrug users, so this pattern appears to be the norm, rather than just misuse of a single drug. Polydrug use occurred in one-third

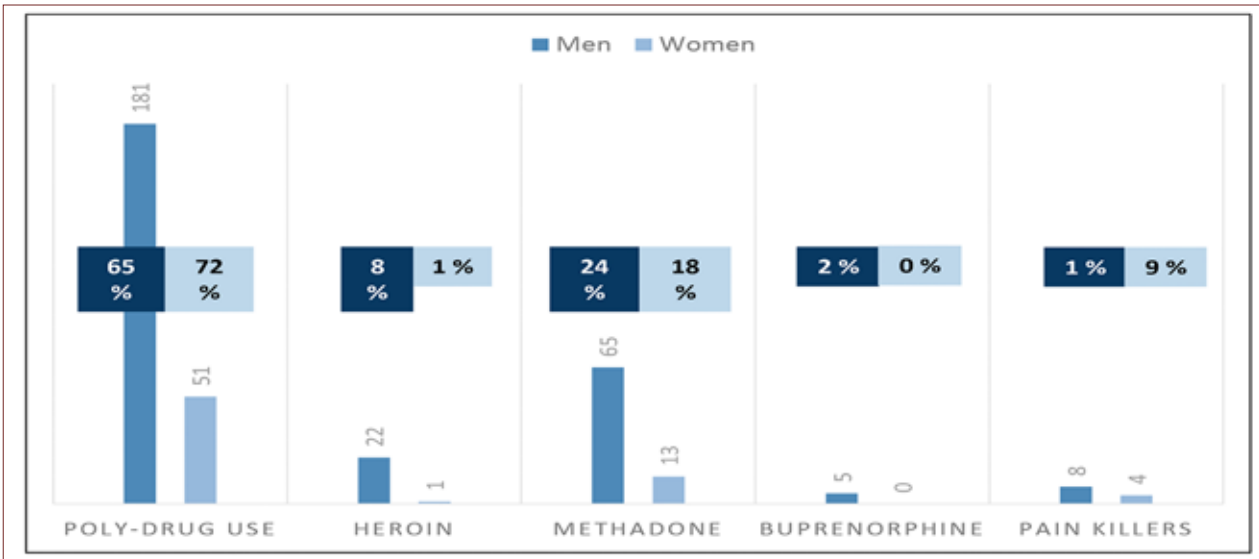


Figure 4. Gender distribution in opioid use, according to the type of opioid, in a 4-year period (2016-2019)

of the patients with painkiller dependence – a lower frequency than among other opioid addicts, but still noteworthy. These results match with previous reports and remind us to pay more attention to polydrug use. Early interventions and management strategies are needed to prevent polydrug use among opioid users **[33]**.

With regard to differences between the patterns of drug dependence found for men and women, our findings were consistent with the research literature. Other studies have found that men and women have different vulnerabilities to various substance use disorders, including opioids **[24]**, and that women are more likely to use prescription opioids rather than heroin, compared with men **[16, 27]**. In our sample, the numbers of opioid-dependent men were about three times greater than women, and there were more men in each of our categories of opioid use. However, the proportions of women with painkiller dependence and with a pattern of polydrug use were higher than for men.

Limitations

The present study does have limitations. Firstly, it is a descriptive, retrospective observational study based upon case note diagnoses. It is possible that some types of drug use, e.g. resorting to synthetic opioids, have been underestimated. Secondly, the study used a sample from a hospital inpatient unit and is therefore likely to be biased towards the most severe cases. Thirdly, the numbers of patients in some categories, notably those with painkiller dependence, were small, so any inferences must be somewhat tentative. On the other hand, the sample was selected over a 4-year period and included 350 patients with opioid dependence. The numbers were sufficient to allow changes in patterns of use to be observed over the study period. The region where the study was conducted is likely to be sufficiently representative of other parts of Europe.

It is clear that the whole field of drug misuse is rapidly evolving and that opioid dependence is a major worldwide public health issue. Not only are there new substances available for people to misuse, but profound changes are occurring in the emerging new drug marketplace. The old face-to-face system is slowly giving way to a new model involving global computer technology, the 'darknet', and overseas manufacturers **[21]**, which makes drug dealers and their customers harder to track and control. Drug misuse services face a constant struggle to catch up with these developments and therefore research that reports on the performance of services is of critical importance.

5. Conclusions

- A total of 795 cases (611 men and 184 women) were admitted to the Dual Diagnosis Unit of Salamanca from January 1, 2016 to December 31, 2019.
- The percentage of cases with an opioid-related disorder remained more or less stable over this period of time (42%-47%). There has, however, been a rebound in the numbers of patients treated for the use of heroin and/or painkillers in the sample studied over the last four years.
- Polydrug dependence was the most frequent practice among patients with opioid dependence (rising from 57% in 2016 to 84% in 2019).
- The number of men was almost three times that of women. Moreover, the numbers of men exceeded women regardless of the type of opioid used.
- The number of patients dependent on painkillers was small, but it increased progressively from 2016 to 2019. The most common indication for opioid prescriptions was cancer. These patients had a slightly higher mean age than the sample as a whole, and they had high levels of psychiatric comorbidity (anxiety, depression, personality disorder). As the prescribing of opioid painkillers has become increasingly common, this type of drug dependence is likely to increase and warrants continued attention.

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Contributors

Design (N.M.C-E., C.R., A.A-N, MA.G.), bibliography review (N.M.C-E., M.T.L-L, S.G-L), data collection and analysis (N.M.C.-E., J.I.I.-L.), writing of the first manuscript (N.M.C.-E.) and final review of the draft (N.M.C-E., C.R., T.D.).

Conflict of interest

Dr. Nerea M. Casado-Espada has received an economic award from Janssen in an oral communication contest and has received fees to give lectures from Sanofi. Dr. Sinta Gamonal-Limcaoco has received fees to give lectures from Sanofi. Dr Javier de la Iglesia-Larrad has received fees to give lectures from Sanofi. Dr Carlos Roncero has received fees to give lectures from Janssen-Cilag, Ferrer-Brainfarma, Pfizer, Indivior, Lundbeck, Otsuka, Servier, GSK, Rovi, Astra, Gilead, MSD, Sanofi and Exeltis. He has received financial compensation for his participation as a board member of the Janssen-Cilag, Lundbeck, Gilead, MSD, Mundipharm, Indivior, Exceltis and Martindale board. He has participated in the PROTEUS project, which was funded by a grant from Reckitt-Benckisert/Indivior. He received two medical education grants from Gilead. None of the other authors declare any conflict of interest.

Note

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Take-home naloxone carriage among opioid users in Lanarkshire

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Summary

Background: Naloxone has been used widely as a means of reducing opioid overdose related deaths. Despite the wide distribution of naloxone kits among drug users, limited understanding exists as to how naloxone is perceived and carried amongst different populations of drug users. **Aim**s: To assess naloxone carriage rate among drug users in Lanarkshire, Scotland. To additionally examine drug users' knowledge about wider aspects associated with naloxone use and storage. **Methods**: A cross sectional survey of addiction service users, using a 10 item semi-structured questionnaire which was administered by addiction service workers during autumn 2016. **Results**: 310 individuals were surveyed. The majority (n=179, 58%) had retained the naloxone supplied to them. 21 reported to be carrying their naloxone at interview (11.3%), 43 (24%) reported not having their naloxone available the last time they used drugs. When asked where their naloxone supply was, the most commonly reported place for storing their naloxone was 'Home' (n= 129, 72.1%). Conclusion: The low carriage rate of naloxone among drug users suggests that wide distribution and current training programmes are not being sufficiently heeded, and for take-home naloxone programmes to succeed further research at both individual and system levels is required.

Key Words: Naloxone; drug users; carriage; opioid; Lanarkshire

1. Introduction

Drug Related Deaths (DRD) are a growing concern worldwide with deaths from overdose, mainly driven by opioids continuing to increase **[1, 3, 10, 12, 14, 22, 37]**. The World Drug Report 2019 **[36]** stated that in 2017 there were 585,000 DRD, with 42 million years of "healthy life" lost as a result of the use of drugs; 2/3 of these attributable to opioids **[24, 25] [9, 23]**. Locally, the most recent report of DRD in Scotland has shown a rapid increase in the number of deaths and has recorded the largest number of DRD ever at 1,187 in 2018, in which opioids potentially contributed to 1,021 deaths; 86% of the total. Males accounted for around 72% of all deaths, the overall majority were aged between 35 and 54 years **[21]**. Despite harm minimisation services and a focus on getting people into treatment, trends in local opioid related deaths continue to increase, suggesting that more approaches, like take-home naloxone (THN), should be considered **[2, 4, 6, 31]**.

Naloxone is the drug of choice for the reversal of opioid overdose due to its high specificity for opioid receptors. It can be safely administered to an individual who may not necessarily be experiencing an opioid overdose **[38]**.

Naloxone distribution to opioid users was first proposed by Strang and Farrell **[32]**, but only taken seriously by service planners/managers in 1996, due to rising deaths from opioid overdoses **[31]**. In 2005, regulatory modifications to licensing significantly increased the extent to which naloxone could be used to prevent deaths from opioid overdoses as it was added to the list of emergency medications that could be administered (by anyone) for the purpose of saving life **[20]**. At the same time, DRD in Scotland were increasing and the Scottish Government effectively challenged Alcohol and Drug Action Teams to reduce

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the number of local deaths. A subsequent report from the National Forum on Drug Related Deaths made the recommendation of establishing a pilot service where THN was provided **[26, 27]**. As a result, since March 2007, both NHS Greater Glasgow and Clyde (NHSGGC) and NHS Lanarkshire (NHSL) Health Boards, with a combined population of 1,860,000 people have piloted THN services. The pilot projects were different in terms of; the formulation of naloxone used, the training delivered and the supply/delivery models for its distribution. In NHS Lanarkshire, a buddy system was used involving a friend or relative, who would also be trained on naloxone administration (accepting the fact that recovery from overdose relies on others administering the naloxone), while NHS GGC delivered a model using group training without the need to have a friend or family member attending **[28]**. 2010 saw the introduction of THN services across all Scottish Health Board areas **[28]**. The Scottish Government, through the Alcohol and Drug Partnerships (ADP), agreed targets for each Health Board to increase naloxone availability to all illicit opioid users. THN supplies are recorded annually and have exceeded all distribution targets set by the Scottish Government **[13]**. In NHS Lanarkshire, in order to increase the supply of naloxone into the community, the Community Prescribing Service introduced an "opt out" for THN for service users.

In order for THN services to be effective, naloxone needs to be available at the time of overdose. This means users need to be carrying naloxone at times of anticipated drug use. However, the practice of naloxone carriage amongst drug users is not well understood, with little published research currently available. McAuley et al. investigated changes in naloxone carriage among people who inject drugs in a nation-wide survey, which revealed a significant reduction in naloxone carriage over time from 16% (2011-12) to 5% (2013-14), the cause of which was unexplained **[18]**.

It is anticipated that studying naloxone carriage will provide a good understanding of how naloxone is managed by service users and the likelihood of naloxone availability during overdose situations.

Aim: The study reported focuses on three particular aspects associated with the routine carriage of naloxone.

2. Methods

2.1. Setting

An estimated 2,000 drug users are currently engaged with the community addiction services in Lanarkshire. All services are delivered in community settings; mainly Health Centres, but some in Local Authority premises.

2.2. Data Collection

A cross-sectional survey design was used to collect data over a 5 day period in the autumn of 2016.

All service users attending appointments during that week were invited to participate in the survey by their 'workers' who were staff working in the addiction services in NHSL; appointments were face to face meetings held at Health & Social Work premises, where prescribing, as well as psychosocial, motivational etc. work was carried out. A 10 item semi-structured questionnaire was administered by addiction team staff to those individuals who agreed to participate. Participation was voluntary and anonymous.

2.3. Data analysis

Frequency analysis based upon demographics was performed on the responses from the closed questions investigating naloxone supply, use, possession and carriage using Microsoft Excel for Mac (Version: 19041401).

Free text responses were analyzed primarily through a thematic analysis by identifying overarching themes to the responses which were then applied into specific categories.

NHSL Research and Development Board were consulted regarding the requirements for ethical approval and agreed that, as this study was a service evaluation, ethics approval was not required.

3. Results

3.1. Characteristics of the study participants

310 individuals agreed to participate from a potential sample of 650 per week, thereby giving an estimated response rate of 47% of service users scheduled to be seen in one week and 15.9% of those accessing services in NHSL as a whole. Males aged between 35-44yrs formed the most prevalent category (n-119, 45%). See **Table 1** for sample demographics.

3.2. Receiving supply of THN

179 (57.7%) individuals reported to have been supplied with THN. The largest proportion of naloxone supply was to those aged 35-44 years (See **Table 1**).

103 individuals reported not having taken naloxone, rather than not being offered it. Of those participants refusing THN, the most common reasons were; "not using opioids" (n= 80%), followed by "not at risk". One respondent said "not got time for training" and another gave a response of "not sure". More participants (182) were aware of the likelihood of get-

Table 1 Patient demographics, including sample size and those supplied with THN

Age	Male	Female	Male Supplied	Female supplied
<25	4	3	1	1
25 - 34	28	25	18	18
35 - 44	90	50	47	34
45 - 54	66	13	36	6
>55	15	6	9	2

ting a resupply of THN than had actually accepted a supply (179).

3.3. Possession and carriage of THN

Low carriage rates of naloxone were evident across all sub-groups. Only 21 respondents possessed naloxone at the time of the interview; of which just over half were female.

83.8% of those not carrying THN on the day of interview stated that they knew where it was, with "kept at home" the most common answer given (86%), followed by 2 respondents each for; "kept with friend", "expired" and "lost".

80 individuals (45% of sample) of the 179 people accepting THN reported having their naloxone with them when they last used drugs. 129 (72.1%) reported storing it/having it 'at home' (usually in the bedroom or kitchen cupboard) as that is the location where they tend to take drugs. "Handbag" was the second most common response (n= 9, 5%) which was exclusively reported by females aged between 35 and 44 years.

43 of those 179 (24%) accepting THN did not have their naloxone the last time they used drugs. The most common reasons were; 'kept at home/forgot to carry it' (n=16, 60%), 'unplanned drug use' (n=4, 16%) and 'lost supply/given away' (n=6, 24%). The remainder of reasons, other than "in the bin" (n=2, 5%) were one off individualized responses such as in my jacket pocket, in the car.

4. Discussion

To the best of our knowledge, no previous study has investigated THN carriage amongst current drug users in Lanarkshire. The study by McAuley et al. **[18]** included drug users from all over Scotland and the randomised controlled trial recruited prisoners from Scotland, England and Wales **[30]**. This study therefore provides a useful baseline for comparison to measure the subsequent rates of naloxone carriage and management in Lanarkshire. Particularly, as the study sample is found to be representative of drug user populations in Scotland, in which males represent more than two thirds of drug users and the majority are aged between 35-55 years **[13]**.

Our findings make an important contribution to the increasing evidence base for THN by exploring naloxone carriage rate among drug users. Results suggest that naloxone carriage rate is low, but the majority of participants knew where it was kept, 'home' being the most frequently reported location for naloxone storage. The low carriage rate of naloxone among drug users (11%) compares relatively well with the carriage rates among people who inject drugs (PWID) assumed by McAuley et al. **[18]** (5-16%), but markedly lower than that found in the N-ALIVE trial (75% in the first four weeks, 50% in the next eight weeks) **[30]**. Madah-Amiri, Gjersing and Clausen have also identified high possession rate of around 37% and the rate was even higher among those who had received training **[17]**. The high possession rates in that Norwegian study might be attributed to the definition of 'naloxone carriage' as participants were not required to carry their naloxone on their person to be in possession of naloxone and may also be due to other factors, such as participants' characteristics, geographical area and formulation of naloxone used (intranasal).

Due considerations would also need to be given to the factors affecting naloxone acceptance that have been expressed by the participants who refused naloxone, as it might be the same factors affecting naloxone carriage. Firstly, perceived risk of experiencing an overdose and current injecting behaviour. The majority of the participants who did not have naloxone reported that they didn't need naloxone as they were not using drugs, were not around anyone using drugs or they didn't feel they were at risk of fatal overdose. Similar findings have been reported by McAuley et al. **[18]** when he explored the potential reasons of naloxone carriage reduction among Needle Exchange Surveillance Initiatives (NESI) responders and by Kestler et al. **[16]** in their analysis of reasons behind refusing or accepting emergency department-based THN.

Secondly, mental illness such as depression, which is highly correlated to opioid use disorders **[8]**, could be of great impact on drug users' decisions of accepting or refusing THN. For instance, one

participant mentioned suicidal thoughts; "I flushed naloxone because I attempted to take my own life and didn't want someone using this on me". Thirdly, one participant refused THN as he did not want to contemplate the possibility of using drugs again. In fact, it has been noted that many drug users who are in recovery or treatment will refuse to possess or carry injectable naloxone as they think that it can trigger a desire to use drugs **[16]**, although it has been accepted that THN does not encourage opioids use **[35]**.

Finally, fear of using injections or needle phobia has been reported by some participants refusing THN. This was surprising as the majority of our participants have been injecting drugs and such a reason was not expected, although this has also been noted by Black et al. **[5]**. This is an area which requires more detailed investigation as it appears to be illogical and hence potentially overlooked by policy makers as a reason for low uptake. Similarly, there are a number of potential reasons as to why carriage of naloxone has been found to be low among NESI participants **[18]** and assumed to be lower eight weeks after release from prison, compared to four weeks post release in the N-ALIVE clinical trial **[30]**.

The majority of the participants in this study reported that they kept naloxone at home as they are mostly injecting drugs at home. The same has been seen in other populations **[7, 33]**. It could be argued that THN might not be effective in preventing overdose related deaths since it is not carried by drug users, however most overdoses occur in residential settings **[29, 33]**. In this case the carriage rate is not representative of the exact availability of naloxone in the case of overdose emergency, but if home was considered as a carriage site for those who use drugs only at home, this would have shown a higher carriage rate.

Naloxone transportability and formulation, which were not explored in our questionnaire, are important key factors to the success of naloxone carriage **[7]**. In the N-ALIVE trial **[33]**, the naloxone kit used was specially designed for the trial to be discreet and portable, which may have contributed to the higher carriage rates. Whereas the kit used in the NESI study and this study was made available via Scotland's National Naloxone Programme is bulkier and less portable. It is feasible that the physical properties of naloxone kits themselves may affect carriage rate. This is an area which should be more deeply investigated, especially when the intranasal formulation has been found to be equally effective in treating opioid overdose, safer in terms of needle injury and generally preferred by families and friends of drug users. Changing to this formulation may increase access to naloxone, especially in the community **[11, 15, 34]**.

Stigma is found to be another reason for the reluctance to carrying naloxone **[7, 18]**. Some participants reported that they wouldn't keep naloxone, "don't want it in my house", with some reporting storing naloxone in a locked cupboard or locked safety box due to issues related to stigma. It would be predicted that the increased awareness of naloxone programmes would break some of these barriers.

Fear of coming into contact with the police whilst carrying naloxone has previously been identified as an issue amongst drug users, mainly the fear of interpreting their naloxone carriage as an intention to use drugs **[18, 39]**. However, none of our participants mentioned 'police fear' as a reason for not carrying naloxone.

Other factors not explored in this study that could affect carriage rates should be investigated including prior negative experience, previous acute withdrawal symptoms, negative peer reactions to naloxone administration, as it is believed that it will 'put them into withdrawal and waste their drugs' **[19]**, and knowledge and nature of training programmes. It has been noted that drug users with higher knowledge scores after training were more likely to possess their THN **[7]**.

This study adds to the published literature but is not without its limitations. The main limitation is recruitment biases in which participants were recruited exclusively from treatment settings, already on treatment receiving methadone or buprenorphine, thereby excluding those not receiving treatment. The use of a questionnaire could have limited the depth of answers that drug users can provide to such a sensitive topic area and as responses were administered by staff, more socially desirable responses related to THN may have been given (recorded). The short, quantitative nature of the questionnaire itself impacts on its utility.

The findings of this study have important implications for harm reduction policy and practice in Lanarkshire and Scotland. They highlight the reasons behind low carriage rates of THN among drug users which should feed into local and national training programmes. In particular, considerations must be given to refresher educational courses for staff and drug users on the benefits of carrying naloxone, changing to different, more user friendly, naloxone formulations and greater public awareness. Additional research, exploring the barriers for carrying naloxone in different geographical areas would be of great interest, knowing that THN programmes operate in different ways across different settings. Further work could also be considered to understand whether carriage rate is likely to be affected by specific participants' characteristics, such as age, gender, education level, marital status, social status and concurrent use of other drugs.

5. Conclusions

Despite increasing adoption of THN programmes and strategies implemented, little has, to date, been done to investigate the extent of naloxone carriage. As one of the first quantitative studies of drug users who have been on treatment, this study identifies the rate of naloxone carriage in Lanarkshire to be around 11% of drug users.

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Contributors

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Ethics

The paper was discussed with Research and Development department at NHS Lanarkshire and it was decided there was no identifiable patient information and the study was a service evaluation, as such ethics approval was not required.

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Point of View

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How supportive and understandable are health care practitioners toward people who use drugs in Albania?

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Summary

Substance use disorders are complex in nature and characterized by impaired functioning and considerable harm caused to the individuals affected and to the society as a whole. Despite the consistent measures on drug use prevention and limits on access to them, a huge number of people still become addicted to drug and need professional help. In order to work, treatment must be easily available, encouraged and offered by motivated and empathic practitioners. Unfortunately, the reality seems to be not so optimistic. Many times the drug user is not just a victim of social discrimination, but he is also a victim of healthcare system stigmatization. In front of the rejection, people with addiction internalize this stigma, blame their selves and refuse to seek treatment. These struggles are much more devastating in small countries such as Albania, with a society in a long transition of norms and moral values. But, how much does it "cost" the life of an addicted person in Albania?! Is a drug user welcomed in the Albanian health system, as is a patient with a chronic disease? Are healthcare providers supposed to be the door where the drug user can knock, when everyone outside tries to make it harder for them to continue living their life?! Too many rhetoric questions that develop in a society where the individuals tend to judge one another, interpret and evaluate each other's behaviour, and inevitably find ways to group together to form ready-made normative categories. For many years in Albania, socially and "legally" accepted individual, were those who didn't t use drugs, or too much alcohol and who always behaved "just like everyone else". People couldn't act and even think 'outside the box'. And health care providers were part of this society.

Key Words: Stigma; Albania; policy-makers; treatment providers

Substance use disorders are complex in nature distinguished by impaired functioning and considerable harm caused to the individuals affected and to society as a whole **[7, 8]**. Despite the consistent measures on drug use prevention and limits on access to them, a huge number of people still become addicts. In all such cases, abstinence from use and unimpeded entry into treatment must be the next step in the process. In order to work, treatment must, in fact, be easily available and encouraged. The health system should have at its disposal all the appropriate facilities, as well as being able to rely on motivated and empathic practitioners.

In the countries that have a long history of substance abuse, such as the USA or several developed countries in Europe, where society has been sensitized and drug consumption is not greatly stigmatized, it is easier to collaborate and treat the drug user **[4, 5]**. Another panorama can be seen in other parts of the world **[6]**, where drug users are often subjected to stigma, even by their own doctors.

What about my country? How supportive and truly understanding are health care practitioners in Albania?! We, medical doctors, are well educated, and well informed. Every day we read about the importance of empathy. But do we stigmatize our drug

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user patients? Going a bit deeper at this point, if they come in our office to ask for help, out of anxiety or due to panic disorder, or episodes of tachycardia or high blood pressure (all of which are very frequent among drug users), do we find time to ask them about alcohol or drug use?! Do we refer them to an addiction specialist?! Or could it be that, just occasionally, we don`t want to complicate our work by coming up with 'embarrassing questions'?

These are some of the many rhetorical questions that I have been putting to myself and asking my colleagues for years. And these dilemmas rush into my head even during these difficult days of the current pandemic. I wonder how difficult it may prove to be for a drug addict to seek help in a health system with low resources and a high level of daily stigmatization.

But the questions don't stop there. Just how much does the life of an addicted person actually 'cost' in and to my country? Should we blame those addicts for what they are? Should we act as their judges? Are we doctors true to our role of being the one and only door where they can knock, when everyone outside the hospital precincts tries to make it harder for them to continue living their life? Several papers compare addiction to other chronic diseases like Diabetes or Hypertension **[2]**. Is a drug user welcomed – a persona grata – in the Albanian health system, in the same way as a diabetic patient? Yes, our suspicions are usually true. These fellow-citizens may look strange sometimes, anxious, too talkative, even paranoid, or reveal shame. But they all have one thing in common. They are silently screaming for help. Our task is to listen to them. If we offer empathy, leaving out the stigmatization, they can open up – for once feel able to show and do their best. Over and over, life has 'punished' them enough, before they ever set foot in our office. It takes time to open up, but once we win their trust, we know we have moved in the right direction.

We need to bear in mind that stigma is not just an Albanian phenomenon **[2]**. As Yang clearly explains: "Stigma can reduce willingness of policymakers to allocate resources, reduce willingness of providers in no specialty settings to screen for and address substance abuse problems, and may limit willingness of individuals with such problems to seek treatment. All of these factors may help explain why so few individuals with SUDs receive treatment" **[3]**. It is well known that, when patients with addiction are approached by providers with disdain and rejection, they may reject the care offered by those providers. Negative behaviours such as these may, in fact, result in a missed opportunity for the addicted person to learn about an important treatment **[1]**. The phenomenon of stigmatization coming from health care professionals in Albania did not develop in a vacuum. We are a part and a product of the society we live in. Individuals tend to judge one another, interpret and evaluate each other's behaviour, and inevitably find ways to group together to form ready-made normative categories. What is more, substance use is a behaviour that is commonly accompanied by a sense of shame or self-stigmatization. So much so that in Albania, for many years, (the when the Communist regime decided everything) we were 'allowed' to praise and promote only one readily available stereotype. The only socially and 'legally acceptable' individuals, were those who didn't use drugs, or more than a modicum of alcohol and who always behaved 'just like everyone else'. People couldn't act and even think 'outside the box'. "Communist governments have traditionally contended that «negative» phenomena, including drug abuse, **[…]** were alien to socialism", explains Kramer in his study **[3]**.

In this reality, it took time to change the stereotypes that had become fixed features of Albanian society over 50 years. Healthcare providers were part of this society, and that fact may go far to explain the long-lasting stigmatization still so often shown towards drug users.

On the other hand, the tight family bonds that consolidated during Communism, and still persist in most of Albanian society, helped to prevent the expansion of drug use in youth. In this case too, as in many others, specific protocols, multidimensional family therapy and well-structured interventions failed to work. Nobody had even heard about them, till very recently. In fact, what really helped the missing elements were just love and care, the best harm reduction interventions in drug use field known to me. As an 'incorrigible idealist', it hurts me when I see that the price my country is paying for becoming a free democracy is making us lose some of our human values.

Be that as it may, we cannot and we should not stop the evolution, despite all the problems we can face, as the weakening of the nation's moral fabric. It is our duty, as healthcare givers, to love our mission by offering compassion and care instead of stigma.

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Covid-19 and addiction: A comparison between Substance Use Disorder patients and gamblers

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Summary

Background: The lockdown Covid-19 pandemic determined lots of clinical and socio-economics consequences. The present study aims to investigating how the lockdown period may have influenced the treatment of patients with a diagnosis of dependence disorder(s). **Methods**: The study was conducted by collecting social and clinical data referring to patients treated in a Unit of the Addiction Service (SerD), within the Local Health Authority of Rome (ASL Rome 1). The sample consisted of 81 outpatients, divided into 38 patients affected by a Gambling Disorders (GD) and 43 patients suffering from a Substance Use Disorder (SUD), according to criteria set out in the Statistical Manual of Mental Disorder (DSM-5). Differences between these groups were calculated using the Chi-squared and Mann–Whitney U tests. The cut-off point for statistical significance was set at $p < 0.05$. **Results**: The results revealed a significant difference ($p < 0.05$) between SUD and GD patients, with respect to the following variables: age, educational level, frequency of treatment, dual disorder clinical picture and post-lockdown abstinence. Moreover, the post-lockdown abstinence proved to be significantly correlated with the following variables: age, occupational condition, and abstinence during the lockdown. **Conclusions**: The study highlighted the fact that patients affected by SUD had greater difficulties in maintaining abstinence than those who suffered from a GD. In particular, from our sample it may be hypothesized that the maturative/cognitive tools linked to older age, employment status and a state of abstinence recorded during the lockdown period function as protective factors with respect to possible relapses.

Key Words: Covid-19; Gamblers; Substance Abuser

1. Introduction

The COVID-19 pandemic is a global public health emergency that has determined a great many clinical and socioeconomic consequences. The World Health Organization (WHO) reported, according to the latest updates, that more than 27 million people have been affected by coronavirus, which has so far caused about 800,000 deaths.

Even though the mortality rate is far lower than those of the Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), that fact alone is not enough to allay the fears of the global population **[10]**.

The lockdown determined social distancing, emotional isolation and economic difficulties that caused specific psychological effects. Among these, the main ones are: post-traumatic stress symptoms (PTSS), depression, anxiety, insomnia, perceived stress, feelings of frustration, aggressive behaviour **[18, 20]**; furthermore, adjustment disorder symptoms (ADS) have increased **[22]**, with the consequent risk of self-medication through the abuse of alcohol and/or psychoactive substances, and with a greater tendency to engage in pathological behaviours (e.g., gambling and internet addiction) **[10]**.

In particular, many studies based on online surveys have shown an increase in anxiety, depression, and stress among the Chinese, Italian, Spanish and Irish populations in response to the COVID-19 pandemic **[1, 6, 9, 17, 25]**. A special kind of Heroin/

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Post-Traumatic Stress Disorder Spectrum had been observed in heroin addicts **[11, 14, 15, 23]**.

Besides several mental health challenges that were expected to be found in the general population **[4]**, addictive behaviours could be potential reasons for major problems during the lockdown period. In particular, one subsequent development that is likely to emerge is that of new behavioural addictions, especially those that are most likely to target teenagers **[3]**.

Unexpected results were, however, found in a multicentric Italian study that investigated craving as a key factor in addiction, and its specific variations between the lockdown period and previous times. One surprise finding was that of lower levels of craving during the lockdown **[4]**. More specifically, craving was higher among outpatients than inpatients.

In addition to the above, through the observations of behavioural addictions, changes in gaming and pornography-viewing behaviours have been reported during the pandemic. While gambling may be impacted in many ways during COVID-19 (the closing of casinos and various types of restrictions on sporting events may have limited certain forms of gambling), internet gambling has always been available, and COVID-19-related stress may have increased people's attachment to gambling **[2]**.

Aim: The aim of this observational study was to evaluate the effect of the Covid-19 pandemic in terms of differences in the type and frequency of the treatments received during and after the lockdown period compared with previous times – a line of inquiry closely related to the clinical picture, especially when a dual disorder was involved. More specifically, we kept track of the patients' ability to stay abstinent over and after the lockdown period, when records were available.

2. Methods

2.1. Design of the study

This observational study was conducted by collecting social and clinical data that referred to patients treated in a Unit of the Addiction Service (SerD), within the Local Health Authority of Rome (ASL - Roma 1) before and during the Covid-19 lockdown period (from March to June 2020), by following events in an online and/or live setting (the latter whenever necessary). A live setting was considered only for patients presenting clinical urgency, in accordance with the therapeutic guidelines.

2.2. Sample

The sample included 81 outpatients (of whom 23 were females) ranging in age from 15 to 77 and an education lasting between 8 and 18 years. It was divided into two subgroups: 38 patients suffering from a Gambling Disorder (GD) and 43 others affected by Substance Use Disorder (SUD), according to the criteria laid down in DSM-5 (Statistical Manual of Mental Disorders-5).

2.3. Data analysis

The clinical and demographic data of patients are reported as mean values, each adding the standard deviation (see **Table 1**). The differences between the two groups – SUD and GD patients –were calculated using the Chi-squared and Mann-Whitney U tests. The variables analysed were as follows: demographic data, type and frequency of the treatment before and during the lockdown, comorbidity (presence or absence of a dual disorder), as well as the continuation or not of abstinence from substance use or gambling behaviour during and after the lockdown. Non-parametric correlations were performed where required in the interests of further significance. Statistical significance was set at $p < 0.05$. Analyses were performed with SPSS 18 (SPSS Inc., Chicago, IL).

Table 1. Demographic and clinical data of patients enrolled

	Addiction study cohort (n 80)	
	Mean (SD)/n	Range (min-max)
Age (years)	41.08 (16,10)	15-77
Gender (female/male)	22/58	-
Educational level (years)	11,39 (3,15)	8-18
Occupational (yes/no)	36/44	-
Patients (SUD/GD)	42/38	-

3. Results

After a previous analysis, one patient was excluded because of the treatment dropout that occurred during the lockdown. The final sample comprised 38 patients with a GD and 42 others who had a SUD (see **Figure1**). The statistical analysis showed a significant difference between these two groups in relation to the following variables: age, educational level, frequency of treatment, presence of dual disorder, and post-lockdown abstinence ($p < 0.05$) (see **Table 2**). The

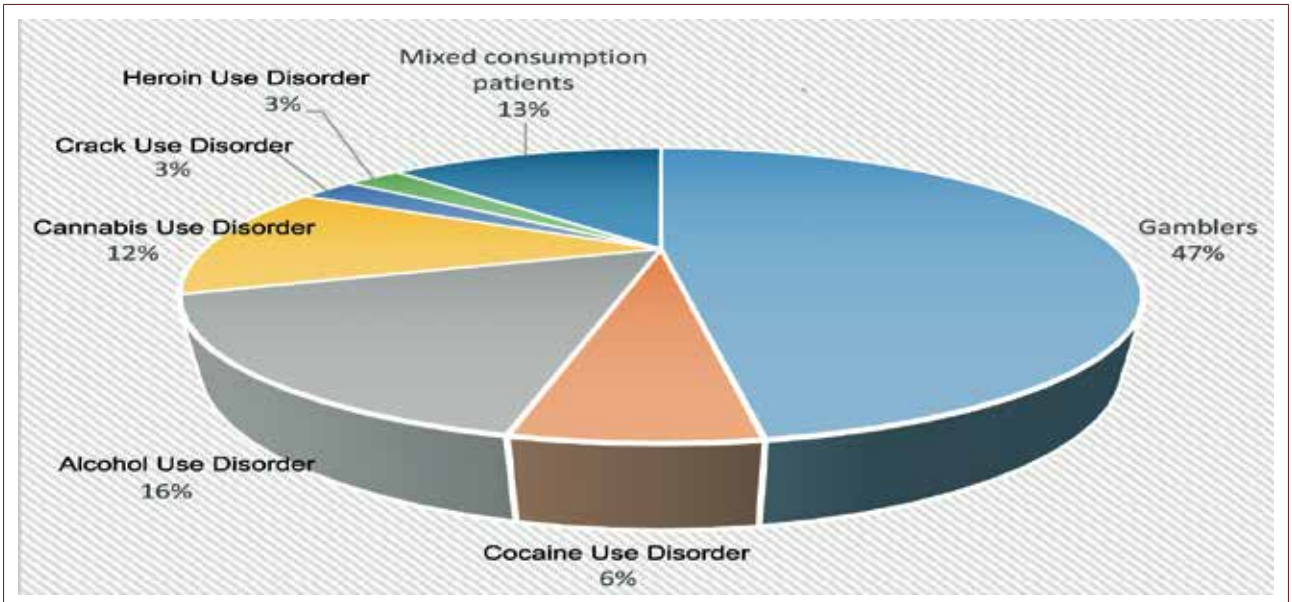

Figure 1. Sample description

post-lockdown abstinence variable, in its turn, proved to be positively correlated with patients' age, employment and abstinence during lockdown ($p<0.05$) (see **Table 3**).

Fifteen patients (18% of our sample) (9 SUD and 6 GD), nine of whom reported a dual disorder picture, did not follow the on-line treatment continuously during lockdown; ten of them, however, did stay abstinent during the lockdown period.

4. Discussion

The present study gave us an opportunity to reflect on the motivation and continuation of the treatment of patients during a period when most types of work were blocked. In fact, during the emergency, the Service had to face many difficulties, especially at an organizational level, and had to readjust by inventing new management methods quickly, in a constructive spirit, for SerD operators and patients alike. In particular, for the same treatments involved (psychotherapy, individual and group psychological support), there was a transition from a personal to online mode which led to the interruption of treatment for about 18% of the sample (who, in most cases, continued with their drug treatment), even if a small minority gave up. In any case, a thorough analysis is called for to clarify these data.

The results showed significant differences, in comparing the data obtained from SUD and GD patients, with respect to their age, educational level, frequency of treatment, dual disorder clinical picture and post-lockdown abstinence variables ($p <0.05$). In particular, the SUD patients were found to have a lower age and cultural level than the GD ones, bearing in mind that these data spring no surprises, if we

Table 2. Differences between groups SUD and GD

	Comparison between Groups	Mean	Z	two-tailed significance
Gender	SUD vs GD	40.56 vs 39.39	-.291	0.771
Age	SUD vs GD	34.89 vs 46.70	-2.271	0.023
Educational level	SUD vs GD	34.48 vs 47.16	-.2.651	0.008
Worker	SUD vs GD	35.07 vs 28.54	-1.608	0.108
Type of treatment	SUD vs GD	42.90 vs 37.84	-1.124	0.261
Type of frequency	SUD vs GD	44.22 vs 35.45	-2.002	0.045
Dual disorder	SUD vs GD	33.64 vs 48.08	-3.270	0.001
Abstinence during lockdown	SUD vs GD	40.95 vs 40.00	-.211	0.883
Abstinence post-lockdown	SUD vs GD	45.14 vs 35.37	-2.340	0.019

SUD= Substance Use Disorder; GD= Gambling Disorders

Table 3. Abstinence post-lockdown

	Comparison between Groups	Mean	Z	two-tailed significance
Age	A vs NA	44.71 vs 31.24	-2.405	.016
Educational level	A vs NA	42.93 vs 35.16	-1.507	.132
Gender	A vs NA	29.24 vs 41.64	-.557	.578
Worker	A vs NA	28.95 vs 39.38	-2.108	.035
Type of treatment	A vs NA	40.64 vs 40.20	-.090	.928
Type of frequency	A vs NA	38.95 vs44.70	-1.418	.156
Dual disorder	A vs NA	40.50 vs 40.50	.000	1
Abstinence during lockdown	A vs NA	35.27 vs 52.00	-3.447	.001

A= Abstinence post-lockdown; NA = Not Abstinence post-lockdown

keep in mind that some types of drugs have low costs and easy access, even for people who have no stable source of income, and that management of the substance is often illegal in nature, so that it can be had free of charge by entering into illicit circles. At the same time, SUD patients showed a higher frequency of dual disorder, in line with what has been reported in the literature **[4, 5, 7, 8, 12, 13, 16, 19, 21, 24]**. A rather interesting datum is that relating to the fact that GD patients were found to have a greater capacity to follow the therapeutic process consistently and stay in a state of post-lockdown abstinence than the SUD ones. These data were linked to some important variables such as greater age, a job and a state of abstinence already present during the lockdown period. This leads to the following reflections.

Regarding patients with GD, they were unable to gamble, since they no longer had any form of access to gambling; that predicament made it easier to stay abstinent. Despite the fears of the health care professionals, there was no increase in online gambling, which, unlike Slots and VLTs, remained accessible. It was found, based on what the patients themselves reported, that, despite the availability of playing "Scratch and win", the fear of contracting the Coronavirus infection acted as a strong deterrent. The general management of daily activities due to the lockdown has made it possible to reduce the impact with external triggers linked to GD. With reference to patients with SUD, it emerged that not all of them maintained abstinence from substances and continuous contact with healthcare professionals. The most plausible hypothesis is that, with drug therapy available, patients would have less urgency to get access to psychological support; even so, some of the patients who had a complex clinical picture, besides socioeconomic and educationally low levels, had registered a relapse, with the comsumption of substances during the lockdown phase, together with a consequent interruption of contact with the Service. Lastly, it should be emphasized that a significant correlation with age and the presence of a job in the case of patients who maintained post-lockdown abstinence, leads to the hypothesis that the maturative/cognitive tools have favoured reflections including risk assessment, both of relapses and of any infection that may be related to Covid-19.

Limitations

The study shows original results, even if there are a few limitations: a small sample; data provided by a single service and therefore not representative of the outpatient population of those with an addiction problem, besides the absence of standardized questionnaires.

In this connection, it would be useful to be able to draw on data from other Addiction Services with the aim of examining a larger sample, providing follow-up and inserting questionnaires, so as to become better able to clarify the clinical variables that may have an impact on whatever data have been detected.

5. Conclusions

As suggested by our study, it may be hypothesized that there are some variables involved in connection with the capacity to stay constantly in touch with the Service, while maintaining the treatment administered before the Covid-19 phase. To be precise, we observed a significant difference in the respective capacities of the two subgroups to maintain the frequency of treatments administered by the Service, highlighting the fact that GD patients showed a greater capacity to follow the therapeutic process constantly than the SUD ones, besides maintaining a state of post-lockdown abstinence more often than in the SUD group. Also, the capacity to stay abstinence after the lockdown period was correlated with the factor of greater age and the higher educational level, in contrast with the complex clinical picture that led to a discontinuous treatment and a lower level of abstinence after the lockdown period. The latter, according to our data, depends on maturative/cognitive tools

linked to older age and employment status, so that these features could function as protective factors with respect to possible relapses.

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Conflict of interest

All authors have no conflict of interest.

Ethics

Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. The study has ethics committee approval.

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Exploring the Depressive Syndrome of Heroin Use Disorder patients. Relationships between Worthlessness/Being Trapped, Deficit Reward and Post-Withdrawal Syndromes

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Summary

Background. The Worthlessness/Being Trapped (W/BT) is a stable depressive psychopathological dimension and part of the psychopathology specific to Heroin Use Disorder (HUD) found by us in fulfilling our ten-year research plan. **Methods.** Selecting patients from the Pisa-Database we compared W/BT items in 504 depressed patients without a history of substance use (NSU-MD), 125 depressed HUD patients (W/BT-HUD) and 847 non-depressed ones (HUD). We analysed differences in the frequency and severity of W/BT items, at the multivariate level (multinomial logistic regression and discriminant analysis). **Results:** W/BT-HUD patients differed from HUD ones in having a higher frequency of the female gender and in displaying the following syndrome: 'feeling blue', 'worried about sloppiness or carelessness', 'feeling lonely', 'feeling everything is an effort', 'never feeling close to another person'. Conversely, 'worrying too much about things' was more frequent in non-depressed HUD patients. W/BT-HUD subjects differed from MD ones without substance use ones in showing more symptoms characterized by 'worried about sloppiness or carelessness', 'your feelings being easily hurt', 'feeling lonely even when you are with people', 'feelings of guilt', 'your mind going blank', 'trouble concentrating', 'unwanted thoughts, words, or ideas that won't leave your mind', 'feeling blocked in getting things done'. By contrast, NSU-MD patients were made recognisable by the following characteristics: 'feeling lonely', 'feeling of worthlessness', 'feeling tense of keyed up', 'worrying too much about things', 'loss of sexual interest or pleasure', 'blaming yourself for things', and 'feelings of being trapped or caught'. MD and W/BT-HUD patients were differentiated by the higher severity in them of the traits: 'worrying about sloppiness or carelessness', 'feeling lonely', 'difficulty in making decisions', and 'feelings of guilt'. W/BT-HUD patients feel less trapped, more dysphoric, and less sexually disinterested than depressed, drug-free patients. **Conclusions:** The depressive syndrome found in W/BT-HUD patients can differentiate W/BT-HUD patients from drug-free, depressed ones, so further adding weight to the hypothesis of its specificity to HUD. The lack of the usual depressive symptoms in W/BT-HUD patients can lead to an incorrect estimation of depression in HUD patients when those symptoms are not reported.

Key Words: Psychopathology specific to Heroin Use Disorder; Worthlessness/Being Trapped dimension; Depressive syndrome

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1. Introduction

In the previous 10 years, some studies by our research group tried to describe the psychopathology specific to substance use disorder (SUD) **[55]** by clearing up the issue of how this information could be utilised for treatment choice **[50]** or monitoring outcome **[49]**.

We identified five main domains: (1) the "worthlessness, being trapped (W/BT)" dimension that assembles depressive, obsessive-compulsive, and psychotic symptoms; (2) "somatic symptoms (SS)", which is characterized by several somatic and anxious features, and resembles opioid withdrawal; (3) "sensitivity-psychoticism (S/P)", which features psychoticism and sensitivity; (4) "panic anxiety (PA)", which can be described as a fear of travelling by train or bus (agoraphobia), going around alone, sensations of dizziness or fear of feeling sick and the experience of critical anxiety; (5) "violence-suicide (V/S)", comprising aggressiveness against others and/or self-directed aggressiveness with anger, rage and breaking things up **[62]**.

As mentioned above, the SCL-90 factor W/BT brings together depressive, obsessive-compulsive and psychotic symptoms. Treatment-seeking addicts who display depressed mood usually report feelings of uselessness and the feeling of being trapped in a corner. These patients feel abandoned, sad, with no goal or interest; they are excessively preoccupied with difficulties, and report feelings of guilt, while experiencing a low sexual drive, too. Obsessive-compulsive symptoms include difficulties in making decisions, completing a task and concentrating, along with worries about one's ineptitude, an 'empty mind' sensation and an incapacity to dominate one's thoughts. Other symptoms, such as the need to check out actions several times or act slowly so as to avoid making mistakes, are not featured. Compulsions and memory impairment do not appear in any factor. Thought disorders consist of feeling alone even when with other people, the thought that one's mind is not working properly, while never feeling really close to others. Lastly, these subjects report a feeling of inferiority, are easily hurt (interpersonal sensitivity), do not like being alone (phobic anxiety) and often feel nervous and upset ("free" anxiety). On the whole, this factor is essentially made up of depressive, obsessive and psychotic features, dominated by feelings of uselessness and of being trapped in a corner (**Table 1**) **[62]**.

The W/BT syndrome does not seem to be influenced by the continued use of heroin versus detoxification treatment, or by the lifetime presence of psychiatric problems – not even by the kind of substance abused **[16, 74-76]**. It is, however, influenced by age (being more marked in older opioid addicts), by the setting of the treatment and the flow of time **[57, 60]**. Its presence in opioid addiction can be better understood by considering the close link between mood disorders and addiction, in terms of neurobiological background, psychological and psychopathological risk factors, and the epidemiology of the two conditions **[4, 5, 7, 10, 12, 14, 15, 20, 26, 30, 32, 34, 35, 78, 83, 90]**. Actually, the involvement of some brain systems, such as the reward, motivational, stress and inhibitory control systems in the physiopathology of addiction, may justify the presence of symptoms such as worthlessness, feeling lonely, blue, and hopeless about the future. We know that an amotivational status is consistent with the chronic changes observed in the mesolimbic dopaminergic system, including a steep fall in the dopaminergic tone and the activation of the CREB/dynorphine pathway **[7, 13, 18, 28, 29, 38, 43-45, 70]**, as well as in the neuroendocrine stress system, which is implicated both in affective regulation and addictive behaviour **[11, 71, 82, 88, 91]**. Our failure to find any association of this dimension with depression or bipolar spectrum disorders **[56]**, together with the lack of any significant correlation with some aspects of craving-related behaviour **[22]**, is consistent with the presence of an inhibitory component in the reward deficiency syndrome **[7]**. The positive association of this dimension with access to OAT rather than to TC treatment calls into question the severity of addiction-related disruption to various areas of life (e.g., the family, work, legal matters), with inevitable consequences on psychological well-being and the urgent need for recuperation, most easily obtained by OAT. Moreover, consistently with a manageable condition, this dimension seems to be influenced by the flow of time after detoxification, which, again, may link this dimension with the condition of active substance use **[61]**.

In one of our studies, we compared 972 Heroin Use Disorder (HUD) patients with 504 Major Depression (MD) patients on the basis of our five SCL-90 dimensions, with the purpose of estimating the magnitude of the differences, in terms of psychopathological symptoms. We observed that prominent psychopathological domains were more frequent in HUD patients, in particular, "worthlessness and being trapped", "somatic symptoms" and "sensitivity-psychoticism". The "violence-suicide" dimension was more frequent in MD patients, while the "panic anxiety" dimension fails to differentiate between the two groups. The prominent psychopathological groups were the most important factor in significantly differentiating between the two groups, when drawing comparisons on the basis of age, male gender and the severity of psychopathological symptoms. Our results suggested that the five psychopathological dimensions found seemed to confirm the trait, instead of the state, nature of our proposed psychopathology of heroin addiction. In any case, the psychopathologi-

Table 1. Worthlessness/Being Trapped depressive syndrome

	Load
79. Feelings of worthlessness	0.69
22. Feelings of being trapped or caught	0.68
29. Feeling lonely	0.66
30. Feeling blue	0.66
54. Feeling hopeless about the future	0.64
32. Feeling no interest in things	0.63
77. Feeling lonely even when you are with people	0.60
41. Feeling inferior to others	0.57
46. Difficulty in making decisions	0.54
28. Feeling blocked in getting things done	0.53
89. Feelings of guilt	0.53
55. Trouble in concentrating	0.52
71. Feeling everything is an effort	0.52
90. The idea that something is wrong with your mind	0.52
88. Never feeling close to another person	0.50
10. Worried about sloppiness or carelessness	0.48
31. Worrying too much about things	0.47
34. Your feelings being easily hurt	0.45
05. Loss of sexual interest or pleasure	0.44
51. Your mind going blank	0.44
26. Blaming yourself for things	0.43
57. Feeling tense or keyed up	0.43
03. Unwanted thoughts, words, or ideas that won't go away	0.41
75. Feeling nervous when you are left alone	0.40
Eingenvalue	26.8
Variance	29.9

cal symptoms of HUD and MD patients seem to differ quantitatively and qualitatively **[51]**.

Aim: In this study we clustered the W/BT symptoms characterising depressed-HUD patients when compared with non-depressed ones and with NSU-MD ones.

2. Methods

2.1. Design of the study

Information on patients included in the present study comes from three different datasets. Data regarding HUD patients came from two databases. The first included anonymous individual information originally collected for clinical or other research purposes ('Pisa Addiction Dataset') at the Dual Diagnosis Unit, Santa Chiara University Hospital in Pisa, Italy. The second came from 'VOECT-Dataset'. The VOECT (Evaluation of Therapeutic Community Treatments and Outcomes) cohort study was conducted in 8 Italian regions in 2008–2009, recruiting a total of 2,533 patients admitted to a Therapeutic Community (TC) treatment for a substance use disorder **[69]**. Data regarding MD patients were extracted from a 5-year clinical dataset of patients treated at the Department of Clinical and Dynamic Psychology of La Sapienza University, Rome. We did not use specific criteria for including patients in these databases other than the 'wish to be treated' and 'wanting to participate' in future surveys. The patient could decide independently whether to accept or decline inclusion in the database. The decision – whether acceptance or refusal – did not in any way affect the quality of the care the patient received. The patient could withdraw his/her consent at any time without giving any explanation. To fulfil the aims of the present analysis only baseline data were used, implementing a retrospective, naturalistic, cross-sectional comparative design, with a single evaluation of the patients, and with the purpose of estimating the magnitude of differences between the presence and severity of psychopathological symptoms in three different kinds of patients. At baseline, patients already undergoing a pharmacological, psychiatric or psychological treatment were excluded.

2.2. Sample

The sample consisted of 1,476 patients, comprising 1,061 (71.9%) males and 415 (28.1%) females. Mean age was 31.32±7.7 (range; 16-59); 504 patients were diagnosed according to the criteria of DSM-5, as MD patients. Of these, 255 (50.6%) were females and 249 (49.4%) males. Mean age was 33.64±9.1 (range: 18-59). 125 patients were diagnosed according to Maremmani's methodology **[62]**, as predominantly W/BT-HUD patients. Of these, 100 (80.0%) were males and 25 (20.0%) females. Mean age was 31.13±6.3 (range: 18-49). 847 patients were diagnosed, according to the criteria of DSM-5, as HUD patients with a non-predominantly W/BT syndrome. Of these, 712 (84.1%) were males and 135 (15.9%) females. Mean age was 29.97±6.6 (range: 16-59).t

2.3. Instruments

To assess the psychopathological symptoms we used SCL-90 by Derogatis et al. **[23]**.

2.3.1. Symptomatology Checklist of 90 items (SCL-90)

SCL-90 is a self-report rating scale that evaluates the psychiatric and symptomatic behaviours of outpatients. It consists of 90 items, with 5 levels of severity (ranging from a minimum of 'not at all' to 'extremely severe'). It was first developed by Derogatis et al. **[23]**. By including HUD for the first time, the 90 items have been rearranged by our research group into 5 main dimensions, which are viewed as underlying a clear majority of the symptom behaviours observed in individuals affected by this disease. The primary symptom dimensions are: (1) Worthlessness-Being Trapped, (2) Somatic Symptoms, (3) Sensitivity-Psychoticism, (4) Panic Anxiety and (5) Violence-Suicide **[62]**.

These 5 main domains have been primarily validated in over 2,500 SUD individuals **[16, 17, 22, 52, 53, 57, 60, 74-77]**. On the basis of the highest z scores achieved on the 5 dimensions, individuals can be allocated to one of the five groups specified above, which are mutually exclusive. For more details on this classification, see Maremmani et al. **[62]**. Total SCL-90 score (sum of all items), the positive symptom distress index (PSDI) and the number of items rated positively (PST) are global scores that can be calculated from SCL-90.

2.4. Data analysis

To be able to differentiate W/BT-HUD, HUD and NSU-MD patients, while also being able to take into account possible confounding factors, we used multivariate analyses.

We utilised a multinomial (HUD and NSU-MD) logistic regression analysis using the diagnosis of W/BT-HUD as reference criterion and the W-BT syndrome, along with age and gender, as predictors. Logistic regression analysis is a powerful tool in statistically distinguishing between two or more groups of cases. The purpose is to see how effective the discriminating variables are.

A discriminant analysis was used to discriminate groups according to the severity of symptomatology. Discriminant analysis is useful to statistically distinguish between two or more groups of cases. The mathematical objective of discriminant analysis is to weight and linearly combine the discriminating variables in some fashion so that the groups are forced to be as statistically distinct as possible. More importantly, the weighting coefficients serve to identify the variables that contribute most to differentiation along each respective dimension (function). We selected items with a load of 0.30 or more. When more than two groups exist, discriminant analysis becomes more difficult to understand at the intuitive level. Evidence about the group differences can be derived from the group centroids. The group centroids are the mean discriminant scores for each group on the respective functions. The centroids summarize the group locations in the (reduced) space defined by the discriminant functions. So, for example if we have three groups, the first and the second function should serve to distinguish one group from others. We should see, otherwise, that there is considerable overlap among the groups. Discriminant analysis is also a powerful classification technique. By classifying the cases used to derive the functions in the first place and comparing predicted group membership with actual group membership, one can empirically measure the degree of success in discrimination by observing the proportion of correct classifications. This kind of research often has to face a situation where there are more discriminating variables than necessary to achieve satisfactory discrimination. If the researcher wishes to select the most useful of these, the stepwise procedure is recommended. The stepwise procedure begins by selecting the single best-discriminating variable according to a user-determined criterion. A second discriminating variable is selected as the variable best able to improve the value of the discrimination criterion in combination with the first variable. The third and subsequent variables are similarly selected according to their ability to contribute to further discrimination.

3. Results

Females were significantly (χ^2 = 192.23; df 2; p <0.001) better represented in NSU-MD (N=255; 50.6%) patients than in W/BT-HUD (N=25; 20,0%) and HUD (N=135; 15.9%). NSU-MD patients were

statistically (F=37.951; p<0.001) older (33.64±9.0) than HUD (29.97±6.6) and W/BT-HUD (31.13±6.3) ones.

Table 2 shows only statistically significant prominent W/BT symptomatology of MD, W/BT-HUD and HUD patients, considering W/BT-HUD patients as providing a reference criterion.

Compared with non-depressed HUD patients, W/BT-HUD ones were distinguished by the presence of the following depressive syndrome. They were females, feeling blue, worried about sloppiness or carelessness, feeling lonely, feeling everything is an effort and never feeling close to another person. Conversely, non-depressed HUD patients were characterized by worrying too much about things.

Compared with NSU-MD patients, W/BT-HUD ones were distinguished by the presence of the following depressive symptomatology. They were worried about sloppiness or carelessness, with their feelings being easily hurt, feeling lonely even when they are with people, with feelings of guilt, with their mind going blank, having difficulty in concentrating, unwanted thoughts, words, or ideas that won't go away. Lastly, these people have the problem of feeling blocked in getting things done. By contrast, NSU-MD patients were marked out by the following stereotype. They spent much of their time feeling lonely, up against feelings of worthlessness, feeling tense or keyed up, having to worry too much about things, with loss of sexual interest or pleasure, blaming themselves for things, and upset by feeling being trapped or caught.

The discriminant analysis (**Table 3**) highlighted two significant discriminant functions. The first was able to differentiate NSU-MD patients (centroid = 3.60) from W/BT-HUD (centroid =-1.91) and HUD (centroid =-1.93) ones. The second divided W/BT-HUD patients from MD and HUD ones.

The first discriminant function was positively saturated by 'loss of sexual interest or pleasure', 'the feeling of being trapped or caught', 'blaming yourself for things', and 'worrying too much about things'. The severity of these symptoms discriminated MD patients. This function was also negatively saturated by 'worried about sloppiness or carelessness', 'their feelings being easily hurt' and 'feeling lonely even when they are with other people'. The severity of these symptoms discriminated W/BT-HUD from HUD patients.

The second discriminant function was positively saturated by 'being worried about sloppiness or carelessness', 'feeling lonely', 'difficulty in making deci-

Table 2. Differences about W/BT symptomatology in W/BT-HUD patients compared with HUD and MD without substance use ones . Only statistically significant results are reported

	Exp(B)	Lower	Upper	Sig.
Heroin Use Disorder patients	1.00			
30-Feeling blue	1.49E-08	5.17E-10	4.29E-07	<0.001
10-Worried about sloppiness or carelessness	0.32	0.13	0.76	0.011
29-Feeling lonely	0.40	0.18	0.91	0.029
71-Feeling everything is an effort	0.51	0.26	0.99	0.047
88-Never feeling close to another person	0.53	0.30	0.91	0.021
Female Gender	0.58	0.34	0.99	0.046
31-Worrying too much about things	1.93	1.10	3.37	0.022
Major Depression without substance use patients	1.00			
10-Worried about sloppiness or carelessness	0.001	7.24E-05	0.01	<0.001
34-Your feelings being easily hurt	0.003	0.0001	0.05	<0.001
77-Feeling lonely even when you are with people	0.004	0.0001	0.05	<0.001
89-Feelings of guilt	0.005	0.0001	0.08	<0.001
51-You mind going blank	0.01	0.001	0.15	<0.001
55-Trouble in concentrating	0.02	0.002	0.16	<0.001
3-Unwanted thoughts, words, or ideas that won't go away	0.07	0.011	0.49	0.007
28-Feeling blocked in getting things done	0.09	0.011	0.79	0.030
29-Feeling lonely	17.32	1.218	246.19	0.035
79-Feelings of worthlessness	31.16	3.098	313.41	0.003
57-Feeling tense of keyed up	41.16	2.797	605.52	0.007
31-Worrying too much about things	2,157.78	57.49	80,988.88	<0.001
5-Loss of sexual interest or pleasure	3,662.75	60.984	219,987.39	<0.001
26-Blaming yourself for things	21,798.92	146.282	3,248,469.15	<0.001
22-Feelings of being trapped or caught	78,754.86	707.866	8,762,005.87	<0.001
Statistics: χ^2: 1918.70; df 52; p <0.001				

Table 3. Differences between MD, HUD/MD and HUD patients regarding the severity of SCL-90 W/BT items. Only statistically significant results are reported

	NSD-MD N=504	W/BT-HUD N=125	HUD N=847			
	M±sd	M±sd	M±sd	F	DF1	DF2
5-Loss of sexual interest or pleasure	2.90±0.8a	1.35±1.2b	0.95±1.1c	522.05*	.37	-.01
10-Worried about sloppiness or carelessness	0.29±0.6a	2.33±1.0b	1.52±1.2c	294.70*	-.34	.34
22-Feelings of being trapped or caught	2.86±1.0a	1.04±1.2b	0.83±1.1b	532.95*	.44	-.20
26-Blaming yourself for things	2.78±1.0a	1.62±1.2b	0.97±1.0c	422.29*	.33	.13
29-Feeling lonely	2.89±1.0a	2.57±1.2b	1.47±1.3c	224.19*	.28	.42
31-Worrying too much about things	2.82±1.1a	1.62±1.2b	1.27±1.2c	255.65*	.31	-.17
34-Your feelings being easily hurt	0.33±0.7a	1.58±1.1b	1.14±1.1c	128.86*	-.33	-.10
46-Difficulty in making decisions	0.46±0.8a	1.92±1.1b	1.14±1.1c	124.57*	-.09	.36
77-Feeling lonely even when you are with other people	0.32±0.7a	1.74±1.1b	1.05±1.1c	126.96*	-.35	.02
89-Feelings of guilt	0.57±0.9a	2.45±1.2b	1.52±1.2c	522.05*	-.26	.34
DF1 centroids	3.60	-1.91	-1.93			
DF2 centroids	-0.00	1.25	-0.18			

Statistics: DF1: Wilks' Lambda=0.10; df 40; p <0.001
DF2: Wilks' Lambda=0.87; df 19; p =0.000
Cases correctly classified: 90.4%

sions' and 'feelings of guilt'. It was the severity of their symptoms that discriminated W/BT-HUD patients from other types of patient.

4. Discussion

Table 1 shows a number of depressive symptoms belonging both to the NSU-MD syndrome and to the W/BT-HUD syndrome. The W/BT psychopathological dimension also includes the item 'feelings of guilt' which is not normally included in any of the standard dimensions in the SCL-90 questionnaire, considering standard factor analysis. The symptom 'feelings of guilt' does not correlate with the depressive symptoms listed in the W/BT dimension. This item appears to be a specific symptom included in the depressive syndrome of W/BT-HUD patients rather than a depressive MD symptom. MD and W/BT-HUD patients share as many as 10 items, considering the whole dimension of symptoms: 'Feelings of worthlessness', 'Feeling of being trapped or caught', 'Feeling lonely', 'Feeling blue', 'Feeling hopeless about the future', 'Feeling no interest in things', 'Feeling everything is an effort', 'Worrying too much about things', 'Loss of sexual interest or pleasure', and 'Blaming yourself for things'. On the other hand, 3 depressive symptoms listed in SCL-90 are specific to the depressive MD syndrome and fail to show any correlation with the W/BT-HUD syndrome: 'Feeling low in energy or slowed down', 'Thoughts of ending your life', 'Crying easily'. Finding none of these 3 symptoms during the clinical evaluation of HUD patients should not rule out a diagnosis of depressive syndrome in HUD subjects. 'Worrying too much about things' is a depressive symptom, but its presence is actually more frequent in non-depressed HUD patients. On the other hand, W/BT-HUD patients show psychopathological symptoms that are not only related to a merely depressive clinical picture, but also linked to various affective dimensions, such as emotional reactivity/interpersonal sensitivity ('never feeling close to another person') and affective resonance with the consequences of their clinical condition ('Worried about sloppiness and carelessness'), suggesting that these two subdimensions may be important features of the depressive syndrome in W/BT-HUD patients. What is more, in these patients the presence of a cognitive dimension related to the affective resonance features is also confirmed by the high saturation found in the symptoms 'feeling blue' and 'feeling lonely'.

Unsurprisingly, W/BT-HUD patients shared their depressive syndrome with NSU-MD ones, but, according to our results, some symptoms turned out to be more frequent and more severe in W/BT-HUD patients, and some others in MD ones. In particular, 'feelings being easily hurt', 'feeling lonely even when you are with other people', 'feelings of guilt', 'the mind going blank', 'trouble concentrating', 'unwanted thoughts', 'words, or ideas that won't leave your mind', 'feeling blocked in getting things done' identified W/BT-HUD patients. Conversely, 'feeling lonely', 'feelings of worthlessness', 'feeling tense or keyed up', 'worrying too much about things', 'loss of sexual interest or pleasure', 'blaming yourself for

things', 'feelings of being trapped or caught' were more representative of MD patients.

On the basis of our results, there are other clinical considerations that now need to be discussed. Compared with MD patients, W/BT-HUD patients show statistically significant differences in the psychopathological items related to the cognitive subdimension of depressive pictures. In particular, W/BT-HUD subjects tend to show a high degree of affective resonance with the consequences of their clinical condition ('Worried about sloppiness and carelessness', 'Your mind going blank', 'Feeling blocked in getting things done'). In addition, W/BT-HUD patients show statistically significant differences in the affective subdimension associated with emotional reactivity/interpersonal sensitivity; in particular, they tend more often to experience the symptoms 'feelings being easily hurt' and 'feeling lonely even when you are with other people'. Moreover, the high saturation encountered in W/BT-HUD patients in the symptoms 'unwanted thoughts, words, or ideas that won't go away' and 'trouble concentrating' seems to suggest the tendency to experience obsessive thoughts and deficiency in attentional focus more frequently than in depressed patients. On the other hand, W/BT-HUD patients tend to experience deficiency in infuturation less frequently than their depressed peers.

Interestingly, the depressive symptom 'Loss of sexual interest or pleasure' seems not to be specific to the W/BT-HUD depressive picture. This result has been observed in previous studies. More specifically, Baharudin et al. found that there was no significant correlation between depression and erectile dysfunction among men in Methadone Maintenance Treatment (MMT), suggesting that the causal relationship between depression and erectile dysfunction is probably bidirectional **[3]**. It has also been assumed that depression may be a consequence of erectile dysfunction or that, vice versa, depression may cause erectile dysfunction **[79, 84]**. Past studies showing data on depression and erectile dysfunction are inconsistent. Spring et al. found that patients in MMT with a lower Derogatis Sexual Functioning Inventory score had a higher level of depression on the Hamilton Rating Scale. They concluded that the sexual dysfunction recorded may have been due to psychiatric problems rather than to treatment with opioids **[87]**. Our findings are consistent with those earlier findings, besides suggesting that sexual problems are more specific to MD patients than to W/BT-HUD ones.

With reference to the severity of depressive psychopathology, the results of our study reveal some coherence with the data regarding the frequency of the symptoms found. In particular, W/BT-HUD patients show not only that they experience symptoms related to the cognitive subdimension of depression more often than the MD patients and the HUD ones, but also that they tend to display those symptoms in a more severe way ('Worried about sloppiness and carelessness'). In other words, 'Worrying about sloppiness or carelessness' (both in its frequency and severity) was the most important symptom in differentiating W/BT-HUD patients from their non-depressed peers, but also from depressed patients without a history of substance use. It should be pointed out that the symptom 'Worrying about sloppiness or carelessness' tends to be most specific to a clinical variant of depression that seems to affect heroin addicts.

It is worth adding that, when W/BT-HUD patients are compared with NSU-MD ones, our study has shown that some depressive symptoms tend both to be more frequent and more severe. In particular, W/BT-HUD patients show not only more frequent, but also more severe symptoms related to the emotional reactivity/interpersonal sensitivity subdimension of depression ('feelings being easily hurt', 'feeling lonely even when you are with other people').

Lastly, the symptom 'difficulty in making decisions' seems to belong to a 'deficiency in decision-making' subdimension that W/BT-HUD patients appear to experience in a more severe way than MD and HUD non-depressed ones.

To sum up, our findings show that W/BT-HUD patients feel less trapped, more emotionally responsive, more cognitively impaired and less sexually disinterested than depressed, drug-free patients. Moreover, the clinical impact of the two depressive subdimensions 'emotional reactivity/interpersonal sensitivity' and 'cognitive/affective resonance' tend to be more severe in W/BT-HUD patients than in depressed, drug-free ones. The depressive syndrome of W/BT-HUD patients can differentiate W/BT-HUD patients from drug-free depressed ones, so confirming its specificity to HUD. These findings seem to be consistent with the concept that W/BT-HUD patients experience a clinically different variant of MD.

4.1. W/BT Syndrome and its relationship with the Reward Deficiency Syndrome and the Post-Withdrawal Syndrome

Looking more deeply now into the depressive psychopathology that is most likely to be found and is most severe in W/BT-HUD patients, we may assume that, from a clinical viewpoint, some clinical features appear to overlap with the symptoms of the "Reward Deficiency Syndrome".

The Reward Deficiency Syndrome (RDS) is a brain disorder distinguished by a clinically significant deficiency of Dopamine (DA) in the brain's Reward Circuit – more specifically, the midbrain and prefrontal cortex. It is primarily acquired genetically, but may otherwise result from prolonged stress **[9]**, and is caused by a decreased DA sensitivity in the

areas of the brain that are involved in the mediation of encoding for attention, reward expectancy, disconfirmation of reward expectancy, and incentive motivation **[31]**. It has been suggested that individuals with a hypodopaminergic state are at risk of seeking reward from RDS behaviours to satisfy their lack of natural rewards **[19]**.

Core symptoms of the RDS are the loss of emotional reactivity, drives and aims, and the inability to experience or anticipate any pleasure **[7]**. In other words, what is clinically relevant in people with RDS is a sort of hedonic dysregulation – or anhedonia. Anhedonia is a condition that leads to loss of the ability to experience pleasure in response to natural reinforcers like food, sex, and exercise, and social activities **[31]**. It has been shown that anhedonia, when accompanied by hyporesponsive reward circuits **[89]**, is an important characteristic of many neuropsychiatric syndromes, such as Substance Use Disorders **[8]**.

On the other hand, the clinical features shown by W/BT-HUD patients appear to resemble the Post-Withdrawal Syndrome (PWS) described by Martin as an enduring pathological state in abstinent detoxified opiate addicts **[64, 66, 67]**, and clinically described, more recently, as a late-onset condition in HUD distinguished by protracted abstinence from heroin use. PWS features some psychopathological symptoms such as feelings of hypophoria (lack of drive, motivation and reactivity with respect to what that individual regards as being satisfactory), dysphoria, extreme sensitivity to pain, inability to complete even simple tasks, and inability to experience pleasure through recreational or natural stimuli (i.e. precisely what is meant by the term 'anhedonia') **[68, 81]**.

Hypophoria and anhedonia are two distinctive clinical features of the PWS. Within the framework of the 'three-stage model' of toxicomanic history, it has been demonstrated the hedonistic-euphoric dimension, which was prominent at the beginning, tends to be gradually replaced by a counterpolar state, which is, precisely, distinguished by anhedonia and hypophoria. From a withdrawal-related point of view, through each detoxification cycle the patient passes from the acute withdrawal state (counterpolar to intoxication) to a later and more enduring drug-free state featuring symptoms of hypophoria, which looms as an acquired state of discomfort related to the absence of drug-related stimulation **[46, 59, 81]**.

In other words, at the end of the natural history of addiction, most drug addicts experience a condition of predominantly depressive affective valency, characterized by hypophoria, otherwise known as 'secondary or late withdrawal syndrome' or PWS (alternatively, 'hypophoric syndrome'). This situation persists for a long time and is attributable to a reward deficit which remains at super-criminal levels over time. Moreover, this syndrome closely resembles the subthreshold symptoms of dysthymia and the residual symptoms of chronic bipolar disorder **[1]** and also recalls the symptoms of the RDS described as a sequela of alcohol and stimulant chronic abuse **[42, 48, 59]**, considering that a 'late-onset depressive psychopathological model' may be valuable not only for HUD but also for the natural history of SUD in general, regardless of the related drugs.

4.2. Addiction Anhedonia: Towards a Depressive Syndrome specific to Substance Use Disorder patients

There is an entire diagnostic category in the DSM that is dedicated to substance-induced mental disorders **[2]**. According to this model, the finding of a depressive syndrome in drug addict patients would not only be independent of the presence or absence of a coexisting drug addiction picture; it would be present with clinical characteristics indistinguishable from those of major depression. According to what has been mentioned supra it is clear that this is not actually correct. W/BT-HUD patients, for example, do not seem to share some of the core symptoms expressed by depressed non-drug addicts, such as loss of libido and coarctation of infuturation. In addition, this variant of the depressive syndrome often manifests itself over time, not infrequently following the suspension of the use of opiates (whether illicit or as a medication) **[65, 68]**.

This form of depressive syndrome is distinguished by a variety of neurobiological, clinical and prognostic features unlike those of major depression. W/BT-HUD patients experiencing a prominent depressive syndrome feel less trapped, more emotionally responsive, more cognitively impaired and less sexually disinterested than depressed, drug-free patients. These symptoms are more severe and more frequent in W/BT-HUD patients than in depressed, drug-free ones. What is more, the anhedonia they experience seems to differ in its features from that experienced by depressed, drug-free patients. In fact, it develops in parallel with the whole unfolding of the addiction disease **[46, 59]**, and seems to display greater severity too, judging by the greater number of treatment failures than those same patients had previously experienced **[21]**. Possible confirmation of greater severity comes from the fact that it does not always recede in response to treatment with antidepressant drugs, though on this topic the available data are ambiguous and largely depend on the class of antidepressant class prescribed – with imipramine showing the most satisfactory success rate **[33, 40, 54, 72]**. These findings reinforce the idea that the depressive syndrome present in addicts – anhedonia, in particular – would be more the consequence of the addiction process on mood than an episodic symptom linked to an affective

phase. We may propose the idea that this variant of 'anhedonia' related to the depressive syndrome of W/BT-HUD patients is an 'Addictive anhedonia'. That would be consistent with the D2 down-regulation model used by Gold et al. to describe the RDS symptoms **[31]** and with the evidence that D2R availability in the putamen is inversely correlated with years of opiate use **[93]**.

It is also known that specific neurobiological long-term modifications in the reward and motivational system occur in patients with substance use disorder. Among them, the finding of the activation of the transcription factor CREB is of remarkable interest due to the consequently intensified expression of dynorphine, which is a high-efficacy k-opioid receptor endogenous agonist. In recent years, it has been demonstrated that the activation of k-opioid receptor mediates anxiety- or depressant-like, anhedonic or dysphoric effects after either stress or chronic drug exposure **[13, 47, 86]**.

What is more, the neuroendocrine stress system is likewise involved in the regulation of mood in SUD patients **[11, 73]**.

The importance of recognizing this clinical condition in HUD patients lies in the fact it is considered a good indicator of relapse, that it is sensitive to opiate agonists and that it is aggravated by administering opiate antagonists **[27, 37, 58, 80, 92]**. Moreover, this depressive syndrome shows a weaker prognosis than the depressive syndrome of non-drug-abusers **[72]**.

To sum up, the depressive syndrome of W/BT-HUD patients seems to be a specific variant of the depressive syndrome that occurs because of the addiction process. As a result it can neither be attributed to the presence of a Dual Disorder, nor assessed as an independent depressive-anxious picture.

4.3. Therapeutic implications

As mentioned earlier, opioids have been demonstrated to have properties typical of antidepressant medications, so suggesting that opioid use may start as a form of self-medication for depressive symptoms, according to Khantzian's theory **[25, 39, 41]**. This fact supports the endorphinergic hypothesis for dysthymic disorders. According to our V.P. Dole Dual Disorder Research Group (V.P. Dole DD-RG), overstandard long-acting opioid dosages (i.e. methadone up to 120 mg/day) are useful in treating most of the cases of depression in HUD patients.

The use of antidepressant medications should be resorted to only as a partial clinical response to depressive symptomatology in patients receiving a Methadone Maintenance Treatment (MMT). In these patients the risk of relapse is high **[24, 85]**.

Tricyclic antidepressants (TCA) (i.e. imipramine and clomipramine), and dopaminergic agents (i.e. bupropion), and contramid trazodone, are helpful medical resources during methadone tapering, at the end of a successful programme, or, in the first six months following the successful accomplishment of a programme. In the latter situation, those medications play a therapeutic role as anti-hypophoric agents, limiting mild withdrawal symptoms (including protracted withdrawal states, or enduring insomnia) in drug-free subjects in MMT. Clinical trials on the effectiveness of tricyclic antidepressants have given ambiguous results. Despite this, according to our V.P. Dole DD-Research Group), TCA medication dosage of around 150 mg/die may be useful in treating those clinical conditions.

As regards Serotonergic System Reuptake Inhibitors (SSRIs), their effectiveness and safety have been documented by our V.P. Dole DD-RG on subjects displaying recurrent depression by maintaining on average methadone dose of 100 mg/day. SSRI bioavailability rises in methadone-maintained patients. Both fluoxetine and fluvoxamine may increase methadone blood levels significantly (by up to 200%, in the case of fluvoxamine). Therefore, methadone doses should be used carefully, especially when SSRIs are added in the induction phase **[6, 36]**. MAOIs' stimulating properties, which have been documented even in depressed non-SUD patients, make them unfit for use with HUD patients, because of their proneness to misuse.

Interestingly, in one of our recent clinical studies it has been shown that high-dosage trazodone (300 mg/die) might find a clinical use in the post-detoxification phase. We found that trazodone is probably able to improve depressive-anxious symptomatology (and cocaine craving) in Cocaine Use Disorder patients who had, previously. voluntarily stopped cocaine use. Before being treated, these patients showed hypophoric symptoms and were at high risk of early relapse, but 6-month treatment with trazodone showed its capacity to avoid early relapse into cocaine use in these patients **[63]**.

Limitations and questions for future research

The main limitation of our study is related to its method of sample selection. The female gender was not correctly represented in our samples. More specifically, NSU-MD patients had a ratio between males and females of about 1:1, which is not representative of the general population of depressed people.

To a limited degree HUD patients show a resemblance to those of the 'atypical MD' with its mixed picture of psychopathological features, in particular as regards the emotional reactivity/interpersonal sensitivity subdimension. Our MD sample is diagnosed by applying the DSM-5 diagnostic criteria, so that the load rate of 'atypical MD' with 'mixed features' on

the whole sample is left unspecified. Comparing W/BT-HUD symptomatology with that of 'atypical MD' with its psychopathological picture of mixed features would, in future studies, be of remarkable interest, with the objective of specifying the W/BT-HUD syndrome in greater detail.

5. Conclusions

The depressive syndrome of W/BT-HUD patients can differentiate W/BT-HUD patients from drug-free depressed ones – a finding that further suggests its specificity to HUD.

The lack of usual depressive symptoms in W/BT-HUD patients can lead to an incorrect estimation of depression in HUD patients when these symptoms are not reported.

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Caring for opioid drug users during the COVID-19 pandemic – a commentary on the Irish experience

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Summary

The management of COVID-19 disease is threatening health systems globally. People who use drugs, in particular opioid users, have increased vulnerability. Targeted adaptations of opioid agonist treatment (OAT) are required to protect this vulnerable population and the healthcare workers providing services. In this article we describe and discuss the associated evidence for the measures implemented to reduce the risks associated with COVID-19 to Irish OAT services. Irish OAT services have implemented the following measures: reduced supervision requirements, increased the use of virtual patient care, streamlined assessment and induction processes to remove barriers to OAT access, provided home delivery of medications, increased access to naloxone and overdose programmes, targeted health and social interventions for the homeless and reduced our prison population. For now, non-essential services including drug and blood-borne virus screening and hepatitis C treatment have been postponed. Planning and review of Irish OAT services is ongoing so that further adaptations can be implemented as challenges emerge. Rapid adaptation of OAT services is required to reduce the impact of COVID-19 on patients, staff and the general public. Ongoing evaluation of these measures is critical since many of these changes may have an enormous impact on health and social care outcomes and be cost saving in a post-COVID future. Furthermore, these positive changes may address some of the social and health inequalities experienced by so many.

Key Words: Opioid agonist therapy; OAT; COVID-19

1. Introduction

Novel coronavirus disease (COVID-19) is a rapidly evolving threat that is challenging health systems worldwide. At the time of writing, there are almost one million confirmed cases and over 50,000 deaths globally **[22]**. Older people, males and healthcare workers are disproportionally affected.

Ireland, like other European countries, is struggling to contain and manage this pandemic. The first case of COVID-19 was identified in Ireland on 29th February and within a month there was over 4,000 confirmed cases and 120 reported COVID-related deaths **[11]**. Ireland was quick to respond to WHO guidance on the management of COVID-19 and implemented school and business closures at an early stage. Irish public health experts have expressed satisfaction at the public's compliance with social distancing and self-isolation measures. These efforts appear to be flattening the curve with reduction in the rates of new infections **[11]**. However, concern has been expressed about the levels of and delays in testing, and the capacity of our hospital and community services to cope with the expected surge in new cases.

The global burden of disease due to opioid use is increasing. Worldwide, there are an estimated 26.8 million people opioid dependant resulting in over 86,000 deaths annually **[3, 4]**. People who use opioids (PWUO), in particular people who inject opioids (PWIO), have increased physical and mental health care needs that make them a particularly vulnerable population during this pandemic **[3]**. They are also at increased risk of homelessness and imprisonment, factors which impact negatively on their ability to

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social distance and self-isolate [3]. There is an increased prevalence of HIV and Hepatitis C infection among people who inject drugs further increasing their vulnerability [4]. To date there is no reports on the impact of COVID-19 on PWUO but it is reasonable to expect that it will be considerable.

It is recognised that opioid agonist treatment (OAT) is a safe and effective treatment that reduces illicit use, the transmission of blood borne viruses (BBV) and mortality and improves mental and physi- cal wellbeing [19]. Engagement and retention in treatment improve outcomes with disruption in OAT (particularly on release from prison) associated with increased risk of overdose [19]. There are already many existing treatment deficits for PWUO including inadequate access to OAT, needle and syringe and overdose prevention and naloxone programmes [13]. Maintaining continuity of care and protecting frontline staff have been identified as priorities during this pandemic and drug treatment services will have similar challenges to other healthcare settings.

Ireland like other European countries has a growing cohort of older drug users (over 40), mainly male, many who started heroin injecting in the late 70s and early 80s. Studies show that drug use exacerbates cardiovascular and respiratory disease and accelerates metabolic aging [7]. Older drug users are often more socially excluded, isolated from family, living in unstable accommodation and have higher levels of physical and mental health problems compared to their peers in the general population or younger drug users [7]. Older age and male gender is recognised as a risk of dying from COVID-19 [2].

Aim: To describe and discuss the associated evidence for the measures implemented to reduce the risks associated with COVID-19 to Irish OAT services.

2. COVID response

In response to Covid-19 many Irish OAT services have adapted treatment delivery to reduce the emerging COVD-19 risks. These changes include;

- Reducing OAT supervision requirements
- Adaption of virtual patient care and telemedicine
- Reduction/postponement of non-essential services including drug and BBV screening and Hepatitis C treatment
- Streamlining OAT assessment and induction
- processes to allow easy access to treatment and avoid waiting lists
- Fast tracking of patients requiring isolation onto OAT
- Home delivery of OAT and other medications
- Remote counselling support
- Virtual multi-disciplinary team meetings
- Increasing access to overdose prevention training and naloxone
- Targeted interventions for homeless and more vulnerable including increased access to more suitable accommodation and supports
- Reduction in prison population.

3. Discussion

Rapid adaptation of OAT services is required to reduce the impact of COVID-19 on patients, staff and the general public. Reducing the requirement to attend reduces the potential for transmission and protects frontline staff. Furthermore, it allows easier implementation of social distancing while patients wait/ queue for treatment. Reduction in supervision may increase street diversion and drug overdose, so risk assessment and individualising care are critical. Providing information to patients on OAT related dangers and safe storage may further reduce the risks. Similar to other services, reducing the require- ment for face-to-face care is recommended [12]. Irish OAT services have widely adapted to telemedicine to conduct risk triaging, assessment, reviews and for providing counselling and psycho-social support. Pa- tients have responded well to these changes but hav- ing up-to-date phone contact details and providing phones to those who don't have them is important to maximise the benefits of these changes. While tel- ephone consultations are adequate for most patients, video linking may be more appropriate for sicker pa- tients and for those with greater psychosocial needs [10]. At the time of writing the Irish health service has yet to agree a common platform and do not rec- ommend the use of mainstream video conferencing services for clinical purposes. OAT services have successfully used telemedicine for hepatitis C treat- ment and providing psychological and other supports [5, 14, 16]. Mental health services have also demon- strated success with remote care and of course gen- eral practice was one of the first medical specialities to adapt to its use to manage COVID-19 [10, 23].

Induction onto OST is recognised as a high-risk period for overdose and should be completed with caution [19]. Establishing the diagnosis of dependence and assessing tolerance is critical, as is OAT dosing over the first four days [19]. Buprenorphine has a safer profile than methadone in induction but may be less successful in treatment retention [19]. Prescribers may consider starting on lower methadone doses (e.g. 20mgs) to mitigate the risks associated with more streamlined assessment, reduction in pre-treatment drug screening and reduced levels of supervision. In Ireland patients requiring rapid in-

duction onto OST treatment are placed in units with increased levels of medical supervision.

Many patients attending OAT services will be required or recommended to self-isolate. This will be difficult for both service providers and for the patient. In some instance home delivery may be required. Irish OAT services have developed a homedelivery network informed by local resources, geography and need. Staff have been redeployed from other statutory and non-statutory services and local police (GARDA) have provided risks assessment and support where necessary. Extra telephone support is provided by assigned personnel and arrangements are reviewed weekly at a virtual multidisciplinary team meeting.

It is recognised that OAT patients have high rates of psychological co-morbidities and managing anxiety and stress during this time will be problematic **[1]**. Coping with self-isolation, particularly if managing withdrawals, will be challenging. Many of their traditional face-to-face support networks are no longer available. In Ireland all the residential drug treatment and aftercare services have been closed which provided the opportunity to redeploy staff to provide remote counselling services and supports. Initially patients struggled to adapt but increasingly report satisfaction with this approach.

With reduced OAT supervision, changing drug markets and patients using illicit drugs and alcohol to manage there is a potential for increased opioid related overdoses. This could exacerbate an already existing epidemic **[3]**. In Ireland, like other European countries, opioid related fatal overdoses most commonly occur in older males and involve multiple drugs including alcohol **[20]**. Overdose education and naloxone programmes have shown to reduce fatal opioid related overdose **[21]**. In Ireland we have expanded our overdose prevention and naloxone programmes to mitigate this. Overdose prevention programmes recommend the use of cardio-pulmonary resuscitation and the administration of intranasal or intramuscular naloxone. We modified our training programmes to provide them remotely (tele-medicine) and have removed the recommendations on CPR and use of intranasal naloxone given the potential increased risks **[15]**.

Routine BBV and drug screening, vaccinations and new hepatitis C treatment have been suspended in OAT services. While these may not have an impact in the short term, they may have medium to long-term consequences for our patients. There is little published evidence on the effectiveness of routine drug screening and screening schedules tend to be philosophical and historical within services **[17]**. This present challenge may give services an opportunity to evaluate the usefulness of drug screening and to implement a more evidence-based approach going forward, post-COVID-19. Identifying and managing BBV are a core part of OAT services. Prior to the emergence of CODVID-19 services were upscaling hepatitis C testing and treatment and were working towards the elimination of hepatitis C infection. Lack of testing and treatment, along with reduced supports and access to harm reduction services may increase rates of re-infection and may impact negatively on 'treatment as prevention' initiatives **[8]**.

Healthcare workers are disproportionally affected by COVID-19, with higher rates of identified infection and deaths compared to the general public **[18]**. Staff may experience moral injury and mental health problems as they struggle to allocate resources and balance their own and their families' needs with those of their patients **[9]**. In Italy, 20% of responding healthcare staff were infected by the end of March **[18]**. Health care staff have to deal with mental and physical exhaustion along with the psychological impact of losing patience and colleagues. Access to sufficient and appropriate quality personal protective equipment is a concern. Childcare is also a problem. Every effort should be made to support staff and all reasonable efforts made to manage their concerns. Proactive planning and communication coupled with adequate resources will reduce the stress experienced. It is important to establish regular virtual multidisci- plinary team meetings to allow timely responses to the rapidly changing conditions both locally and na- tionally **[6]**.

While it is natural and important to focus on emergency efforts to manage, treat and develop a vaccine to control this epidemic, it is important to evaluate new models of delivering medical and social care. These models will have been developed at a time of crisis but may have real benefits for patients and our healthcare systems in the future. It is also important to evaluate the potential negative impacts of these new models and make efforts to reduce/eliminate these both in the present and the future. It is important that resources for these evaluations are factored in health budgets as many of these new measures may have very significant health benefits and cost savings in a post-COVID future. We also need to plan for this new reality for our practices.

4. Conclusions

PWUO have health and social risks that make them vulnerable during this COVID-19 epidemic. OAT services can adapt to reduce these risks for this marginalised and underserved population. These measures can have both immediate and future benefits to this group but also inform how health and social care is delivered across our health services. Ongo- ing evaluation is critical since many of these changes may have an enormous impact on health and social care outcomes and be cost saving in a post-COVID future.

Doctors and others working in the area need to advocate for the protection and even the expansion of harm reduction services and linked psychosocial supports during these challenging times.

The Irish health and OAT services have responded in a dynamic and effective way to this challenge. We have implemented new and efficient ways to provide healthcare, reduce our prison population and have introduced sweeping changes to how we care for our homeless and marginalised people. It is my hope that we can take these positive changes and learnings into a post-COVID-19 future and address some of the social and health inequalities experienced by so many.

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Despite repeated criticism, medications (methadone, suboxone) for opioid use disorder continue being called "substitution" treatments

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Summary

Even though its use has declined, "Opioid Substitution Treatment or Therapy" (OST) is still used to describe agonist therapies, viz methadone, suboxone, despite its stigmatizing effects and fundamental inaccuracy. 'Medication Assisted Treatment (MAT) was an earlier, ca. 2000, response to the need to improve terminology, which, in turn, has been superseded by 'medications for opioid use disorder' (MOUD). Yet agonist therapies continue being called 'substitution' treatment at a significant rate: a 2019-2020 online 'verbatim' search yielded 289 'hits' for OST vs 330 'hits', for MOUD respectively, showing the disturbing persistence of a discredited term. This essay explores how the term 'substitution' fails to describe MMT on linguistic and psychopharmacological grounds, its sometimes intentional stigmatizing effects, indirect fatal consequences, underscoring the need to abandon the term. Federal and state government agencies, non-MOUD treatment systems and support groups, treatment accrediting agencies, academics, journals, health services training institutions, international health agencies, and the media, should screen for the term "substitution", eliminate it if found, and use MOUD instead. The goal is to increase the willingness to welcome and implement programs employing agonist medications for OUD as essential to public health and individual recovery, and to view MOUD programs as a key support for the communities where patients are treated.

Key Words: Critique, "substitution treatment", MOUD, stigma

1. Introduction

Having developed a major medication for OUD, methadone maintenance treatment (MMT), V. P. Dole was puzzled by Alcoholics Anonymous' (AA) invitation to join their board as a non-alcoholic trustee **[14]**. He thought the invitation was at odds with AA's emphasis on abstinence and group-supported recovery. He learned later his invitation was part of AA's desire to avoid becoming inflexible about possible helpful interventions for alcohol use disorder. AA founder Bill W. indicated he wanted Dr. Dole to help develop an analogue of methadone for alcoholism because "…he (Bill W.) was thinking about the many …who are lost" **[14]**.

The open-mindedness shown above is disheartening in light of the continuing stigma against MMT despite overwhelming supportive evidence since its mid-1960s introduction **[13, 25]**. Through the 1960s and during its expansion in the 1970s, it was described contemptuously as 'poison', 'garbage', 'genocide'; these were followed by less extreme but still derisive terms, viz "methadone addicts" and especially, "methadonians" **[6, 10]**. Other erroneous characterizations included "it's just another drug", "it's a legal high", and especially, "it's just substituting one drug for another". In a 2005 documentary **[32]**, MMT was called "Methadonia", as if it were an alien world apart. A 2017 **[33]** documentary highlighting the burdens of treatment participation and limited access but highly favorable to MMT in principal, is titled, "Liquid Handcuffs"--sensational, exploitive and paradoxically, a phrase liable to hinder desired institutional change.

The most destructive effect of such attitudes is countless avoidable deaths **[41]**. By 1988, it was

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found that MMT reduced the risk of HIV infection and dying from AIDS [4, 34]. Stigma-influenced regulatory burdens on MMT (a.k.a. opioid treatment programs or OTPs) programs are forbidding (e.g., the CARF [11] accreditation standard manual is over 3.43 megabytes, roughly 750 single-spaced typed pages; nearly two-thirds of US programs seek accreditation from CARF, aside from all programs having to meet extensive federal and state regulations). Along with 'street culture' myths [19], the resulting health system's limitations on access to and availability of OTPs effectively says: it is tolerable that persons with OUD (POUD) become HIV positive (and risk dying of AIDS) or, with greater certainty, an opioid overdose, rather than become MMT patients.

Phrases such as 'Medication Assisted Treatment' (MAT) and 'Medication-supported Recovery' (MSR) reflect positive changes in terminology aimed at countering the stigmatizing effects of 'substitution' as in "opioid substitution treatment". (However, Wakeman [40] and Robinson and Adinoff [35] show MAT itself is ambiguous, invites confusion and may discourage enrollment). Currently, MOUD is the most acceptable way to describe MMT and other agonist OUD pharmacotherapies. Another example of positive change beyond terminology is NY States' recent requirement that MMT (and Suboxone) can no longer be prevented from being offered as a treatment alternative in drug court to arrestees with OUD. The MOUD option had been excluded for the past 52 years [1].

2. MOUD is not Drug "Substitution": An Analysis

How has MMT in particular come to be viewed so negatively, with ambivalence at best. Joseph [24] focused on deviance theory and the roles of race/ethnicity and moral entrepreneurship during the 1920s and 1930s in establishing a punitive stance in the US regarding OUD management culturally and against a medical approach, cf. also [7]. Here, specific uses of language that maintain the stigma are attacked because they are lethal not merely incorrect. Several terms and phrases have been used to stigmatize MOUD especially 'substitution', characterizing MMT in various media and online sites as 'controversial', e.g. [3], and using the diminutive 'just' to express disdain, as in "…just substituting one drug for another", "just a legal high". Here, the focus is on the seemingly ineradicable term "substitution"; while its use has declined, it continues to be used despite being destructive. This review is intended to speed complete abandonment of the term whether the individuals and organizations who use it do so without malicious intent. The author strongly disagrees with those who call MMT, 'opioid substitution therapy' or 'drug substitution treatment'. A. Goldstein [20, 21] and T. Kosten [26], authorities on the neurobiology of opioids, strongly rejected the idea that MMT is a substitution therapy based on the pharmacological and neuroscientific data available through ca. 2002. Gerra, Maremmani et al. [15] have marshalled more recent neuroscientific evidence which is consistent with the earlier work. The data show unequivocally that the pharmacokinetics, dynamics, and psychopharmacology of short acting opioids and long acting agonists, are fundamentally dissimilar precluding their being substitutes for one another. For these reasons, Heroin Addiction and Related Clinical Problems does not accept articles in which is present the term 'substitution' in referring to methadone or buprenorphine treatment [28].

Nevertheless, the term 'substitution' persists in a variety of media including academic journals [36, 42] despite the efforts of editors to preclude use of the term in their article submission policies, the work of advocacy organizations such as SSN [37], and changes in training curricula for healthcare workers. This persistence is shown in the results of an online google search [2] for verbatim or 'exact' 'hits' for "opioid substitution treatment" (OST) compared to "medications for opioid use disorder" (MOUD), for 2019 – July, 2020. Item types covered a variety of written and other media, e.g., manuals, reports, newspaper accounts, government advisories, journal articles, documentaries, movies, websites for OUD treatment providers. The number of hits for OST was 289 and for MOUD, 330, or 47% vs. 53%, hardly showing the disappearance of a discredited characterization of the treatment.

Returning to fundamentals, what is MMT a substitute for? Heroin? People take heroin because they want to get "high" and when use becomes compulsive, continue to, notwithstanding that preventing withdrawal distress ('getting straight') may be more important for (some) long term POUDs. Also, POUDs will get high from other drugs, and alcohol, because at the time, the costs, health, jail and other risks of securing and using heroin were prohibitive. The enormous positive incentive of getting high (the prototypical "rush") specifically from heroin remains a dominant factor in continued heroin use [29]. For those blocked by cost, the potency of the desire to get high from heroin specifically is shown by splitting an affordable bag(s) into two injections, by 'booting' (injecting, reabsorbing the liquid into the syringe, and injecting again), by going into withdrawal or treatment programs, reducing the size of their 'habit', and as a result, making getting high affordable.

The clinically optimal or 'blocking' dose of methadone eliminates the 3- or 4-times/day, major affective changes on heroin ('high'-'straight'-'nearly sick' or 'straight'-'nearly sick'), preventing withdrawal illness, reducing craving, and providing a bar-

rier to intoxication given the cost/availability of sufficient illicit opioids to exceed blockade [13]. Aside from mild, transient effects peaking at 1-2+ hours after their dose (sedative for some patients, stimulating for others), patients are alert and function normally [22, 23] throughout the 24 – 36-hour medication cycle, a counterintuitive finding given the image of somnolence (e.g., "nodding") as a key effect of short-acting opioids.

It is certainly helpful for saccharine to be white, powdered, and not have sugar's health liabilities. However, there must be a compelling incentive to consume it in order for it to be a substitute, and that incentive is that it tastes like sugar; it would not be a substitute otherwise. Only the most willful (and uninformed) detractor would suggest that methadone is experienced ('tastes') just like heroin; methadone simply does not satisfy this crucial requirement. It is useful to consider here that the drug cartels are not manufacturing and distributing huge quantities of methadone because of its desirable euphorigenic properties!

The argument that 'substitute' is stigmatizing rests as well on why they are sought and how they are generally evaluated. Substitutes are sought when the desired item is not available, too expensive, or its continued use comes to have adverse or toxic consequences. Further, use of a substitute is usually viewed as temporary, with the hope, expectation that access to the preferred item is imminent. Embracing a substitute requires that it provides very similar subjective effects as the preferred item. By being comparable experientially but not the same, however, the 'substitute' is typically judged less preferred, an expedient, with the connotation of "second-rate". The negative semantics of 'substitute' are unambiguous.

Empirical support for methadone not being a substitute for heroin, is that it is a relatively uncommon choice of euphorigen for noncompliant MOUD patients; cocaine, amphetamines, tranquilizers, sedative-hypnotics, THC and alcohol are much more common [43]. And while positive toxicologies for opioids are also common, patients' use of methadone by itself is rare; if used by default, it is typically combined with a tranquilizer or sedative-hypnotic. Mintzer's (2007) review [31] is supportive: accident drivers positive for methadone were often positive for a sedative-hypnotic or phenothiazine as well.

The counterargument to the claim that methadone is not a substitute is that substitution simply means methadone takes the place of heroin, relieving withdrawal distress and craving, and exploits or uses the properties of being long acting and administered under medical auspices, to achieve its clinical benefits. MMT, therefore, is a therapeutic 'replacement' of heroin justifying use of the term 'substitution' to describe a therapy, and it is a semantic quibble to object.

Three points here. Gilmore [16] cites literature showing that the terms used to describe people with substance use disorder have adverse effects on treatment seeking, outcomes and preventable mortality—words have powerful health effects. Secondly, when anti-MMT critics and skeptics say MMT 'uses' methadone's properties of cross tolerance with heroin and much longer period of action to achieve its benefits, why are these properties suspect? Thirdly, critics and skeptics often frame "substitution" by preceding use of the diminutive "just"-- "It's just substituting one drug for another": repeated pairing of 'just' with 'substitute' appears intentionally demeaning, an expression of contempt.

One purpose of diminishing MMT is to downgrade its benefits by minimizing the differences between it and heroin addiction—stigma by association [24]. A major reason is to promote a theory of OUD where cessation of use occurs solely by sociobehavioral interventions, without pharmacotherapy, or any treatment, and that supporting MMT (or the MOUD suboxone) entails a morally dubious retreat from what should be done as the alternative theory is 'correct'. Clearly, many POUDs do stop compulsive use with limited or no support [5, 8]. However, the anti-MMT critics ignore or downplay the fact that many POUDs are intractable -- repeatedly resume compulsive use after withdrawal and other non-pharmacotherapeutic interventions (with their significantly increased risk of dying) and through MMT, cease use of illicit opioids, function acceptably, avoid potentially lethal conditions associated with OUD, supporting recovery and making indispensable contributions to individual and public health. Further, as OUD shares major features of chronic illnesses such as diabetes, hypertension, and asthma [30, 38, 39], further reinforces the appropriateness of MOUD, a medical intervention. Heterogeneity in the characteristics, treatment appropriateness, and chronicity of OUDs is hardly a revolutionary idea.

Abstinence adherents used to aggressively promote their 'star' clients while demeaning MOUD to secure support from visiting politicians; stigmatization also has proceeded by deploying the tag 'controversial' [3] (Don't approach, there is risk here) and very recently, by the claim it "over-medicalizes" OUD [27], that addiction is nothing but "deep" learning via repeated contact with a powerful reinforcer, not a disease, not medical at all. The antagonism against MMT is less about clinical effectiveness than jockeying for theoretical notice or maintaining market share for clientele. Labelling MMT "controversial" sounds more like an advertising ploy to get noticed as opposed to an expression of justifiable caution.

Another possible reason arises from envy of Drs. Dole, Nyswander and Kreeks' iconic status in addiction medicine. Well-advertised efforts since

the 1970s were initiated to develop nonopioid OUD withdrawal and treatment medications-- alternatives to methadone **[9, 17, 18]**. The exploitation of MMT and its patients to support research, treatment, and medical business careers may be an underappreciated contributor to stigmatization of MMT.

An interesting confirmation of the stigmatizing effect of 'substitution' is shown by the phrase 'nicotine replacement therapy' (NRT) **[12]**. A stronger argument can be made for 'nicotine substitution treatment': the patch-, lozenge-, or gum-delivered nicotine vehicle substitutes for the smoked vehicle and its carcinogens while using the same dependence- generating ingredient: to stop craving, prevent withdrawal distress, while providing similar subjective effects. A replacement would be a smoked item without undesirable carcinogens containing a non-dependence producing mild stimulant. However, given the financial exigencies of marketing a smoking cessation treatment, 'replacement' is clearly preferable in view of the negative connotations of 'substitution'.

Perhaps, an anecdote provides a more compelling reason to abandon the term "substitution". When a colleague asked an Asian-American patient what he thought of the idea of calling methadone maintenance treatment substituting methadone for heroin, the puzzled patient said through a translator he didn't understand what my colleague was talking about. He said that he took methadone because it was a medication to help him stop using heroin and it did.

3. Conclusion

This essay addressed the stigmatizing effects of the declining though continued use of 'substitution' to describe agonist MOUDs, MMT specifically. Biomedical/neuroscientific authorities A. Goldstein and T.R. Kosten rejected the argument that MMT was a substitution treatment, supported even more convincingly by very recent work reviewed by Gerra, Maremmani et al. Further, the ways 'substitution' and the phrase, 'just substituting one drug for another', have been used were found to be inaccurate on linguistic and psychopharmacological grounds, stigmatizing, and along with other sources of stigma, having lethal consequences. It is recommended that the term 'substitution' be screened for and discarded by federal and state funding and oversight agencies, non-MOUD providers and support groups, addiction medicine and research organizations, researchers, journal editors and publishers, the courts, educational curricula in health care and allied helping professions, international health agencies, and the media. Reducing the stigmatization borne by the language for describing medical treatment for OUD may help reduce barriers to treatment entry and the burdens of treatment participation, ultimately making use of MOUD closer to the management of other recurring health conditions, which is the case for many POUDs.

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