

# Can the Opioid System Offer a Unifying Framework for Addiction

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## Aims

Addiction and drug use bring with them a series of complex problems which confound the formation of avenues of therapeutic intervention, deep understandings and social policy. The realm of addiction studies necessarily involves a search for frameworks which can rationalise not only the self reinforcing properties of substance use, but also how these are entwined with a range of mental illnesses, social practices, polypharmacy and environmental traumas.

With these problems in mind, the aims of my research have been to analyse what prospective unifying frameworks might bring siloed understandings together to provide practical advantage in the field. The aims of this poster are to show how the investigation has converged in the area of opioid physiology.

Addiction and drug use involve clusters of perennial issues which defy simple articulations or solutions. The notion of 'wicked problem' was developed in public administration during the 1970's to identify emerging problems defined as 'complex, involving multiple possible causes, internal dynamics not assumed to be linear, and to have very negative consequences for society if not addressed properly' (Peters, 2017).

Addiction and drug use as human phenomena are tied into the lives of people, and as such cannot be reduced to a simple response without similarly diminishing the individuals which are tied to the phenomena. Any attempt to analyse the success or failures of drugs policy approaches must necessarily be met with an assay of perspectives and situational knowledge which intersect on and in the lives of people. These must be cross referenced with clinical data to humanise our understandings of physiological responses particularly in relation to what constitutes trauma.

Stress responses (Drolet et al., 2001; Valentino & Van Bockstaele, 2015) and experience of pain (Ballantyne, Sullivan, & Mark, 2017; Kapitzke, Vetter & Cabot, 2005) bring about the release of endogenous opioids. This offers an account of how such stimulæ might predispose individuals to drug seeking behaviours in response to psychological anguish.

Addiction and drug use are associated with multi-sector/multiple needs working as, when there is a problem with drug use there is a tendency to find a series of co-morbid problems which are dynamically linked to each other such as mental health (NIDA, 2010), homelessness (Fletcher & Reback, 2017; Smith, North, & Spitznagel, 1993), and physical illness (e.g., HIV, hepatitis C, Tuberculosis) (World Drug Report, 2017).

A problem on the increase is how to assess and manage the issues of polydrug use (EMCDDA, 2009). Practical understandings of multiple drug use and the analysis of overlaps between different drug-using populations are lacking. Cannabis and illicit drug users (World Health Organization, 2016), alcohol users (McCabe, Cranford, Morales, Young, 2006), prescription and OTC medications (Roberts, 2016), along with use of novel psychoactive substances (Tracy, Wood, & Baumeister, 2017) makes for a complex picture which lacks an agreed upon unifying toxicological framework. This is further complicated by the normalisation of psychoactive substances such as caffeine (Uddin et al., 2017) in day-to-day lives of people and the exposure of some populations to subnutritional (Grotzkj-Giorgi, 2009), carbohydrate rich diets (Bonner, Thomson, & Cook, 2019).

The limitations of substance-specific approaches, discipline-specific analyses, or service-specific interventions abut against the emergent aspects of crises in the lives of individuals and communities. Any dialogue in this area has the problem of integrating social and medical models of disability in practical and sensitive ways so as not to overshadow the life and experience of the individual but also to afford a clear sense of how the physiological science is factoring into behaviour.

## Methods:

A cross disciplinary systematic literature review was undertaken to find out how addiction behaviours were apprehended in varying disciplines and through various methodological approaches. I have drawn together findings from different fields of knowledge to coalesce a narrative which can offer insights to identify prospective frameworks to contextualise the lived experience of people who live with problematic substance use.

## Discussion:

The aims of my research have been to analyse what prospective unifying frameworks might bring compartmentalised understandings together to provide practical advantage in the field. The aims of this study are to show how an investigation into various drugs of dependency has converged in opioid physiology and how related psychology can also be understood to be affected via this biochemical system. There is a significant evidence base that the opioid system of the body offers an overarching framework giving a compelling account of mental illness as related to stress, cognitive disorder, the generation of abnormal repetitive behaviours, and compulsive behaviours such as overeating.

Opioid peptides and their receptors have a widespread but selective distribution in the central and peripheral nervous systems, particularly in circuits involved in pain modulation, reward, responses to stress, and autonomic control (Benarroch, 2012). A significant aspect of stress is associated with the biological release of endogenous opioids (substances which act through the opiate system) (Valentino & Van Bockstaele, 1996).

Di Chiara et al (1993) reported that drugs of abuse act on specific neurotransmitter pathways eliciting neurochemical changes that mimic aspects of the overall pattern of the neurochemical effects of natural rewarding stimuli. Thus, drugs of abuse are biochemically homologous to specific aspects of natural rewarding stimuli. Natural stimuli accomplish this result indirectly through their sensory properties and incentive learning while drugs stimulate by a direct central action through the critical biochemical reward pathways.

Many drugs of abuse mimic the incentive properties of natural stimuli and their ability to stimulate mesolimbic dopamine pathways. Drugs might be abused as a result of their action at sites located beyond dopamine or by mimicking other aspects of naturally rewarding stimuli such as the 'functional' (or trophotropic). There is evidence that dopamine receptor stimulation facilitates release of enkephalin (Llorens-Cortes, Zini, Gros & Schwartz, 1991) and dynorphin (Steiner & Gerfen, 1998) from neurons illustrating the close relationship which dopamine has with opioidal physiology.

In the mechanism of the positive reinforcing properties of drugs of abuse, drugs are simply acting on mechanisms and processes that the organism utilizes in its normal functioning. These biological mechanisms are the result of a phylogenesis involved in the adaptation of the organism to the environment. The incentive aspects of natural reward are essential for stimulating behaviour directed to approach and contact with the rewarding stimulus. The incentive properties of natural reward hence increase the probability of contact with the primary reward by conferring, through conditioning, incentive properties to otherwise neutral environmental stimuli ('incentive learning').

This sets up the physiological conditions which afford a tangled hierarchy (Hofstadter, 2006) in situations where trauma related stress activates natural reward systems through the release of opiates. To compound the complexity there is evidence to show that both opioids (Kosten & George, 2002) and neuroleptics (Bortolozzi et al, 2010) stimulate dopamine release creating a positive feedback loop.

## Findings:

There is a granular evidence base indicating that drug use, addiction, mental health and certain behavioural phenomena converge in opioidal physiology. Pharmacologically and biochemically opioids act through the opiate system without necessarily being true opiates.

An account of the social and medical models of mental health might be brought together by further looking at the stress responses which occur as a physiological response to social and physical trauma. For example prolonged confinement is noted to result in abnormal behaviour of stereotypes or inactivity and unresponsiveness. These behaviours have been linked directly with increased opioids and opiate receptor density in the central nervous system (Zanella, Broom, Hunter, & Mendl, 1996).

The release of endogenous opioids create positive feedback which maintains the persistence of the stereotyped behaviour and inhibits switching to different activities (Rushen, De Passillé, & Schouten, 1990). As discussed opioids function both to mimic natural reward signalling in the organism and as a part of the response to trauma, commonly associated with, but not limited to anaesthesia (Di Chiara, Acquas, Tanda, & Cadoni, 1993).

High stress impairs the formation of explicit memories and interferes with complex, flexible reasoning whilst it reinforces performance of implicit memory and well-rehearsed tasks (Sandi, 2013). This offers a potentially useful account of the formation of stereotyped behaviours under conditions of stress. Georgia Mason describes these stereotypes as 'repetitive invariant behaviour patterns with no obvious goal or function' (Mason, 1991). Her work identifies these behaviours in captive animals, mentally ill or handicapped humans, and subjects given stimulant drugs.

Abnormal behaviours which arise through impoverishments and trauma are demonstrations of psychological aberrations. Andrea Lord (2002) presents the idea that such repetitive behaviours are manifestations of mental disorder in the animal world which we see in human beings. She reports that such repetitive behaviours are seen in over 36 different mental illnesses of modern psychiatry including autism, schizophrenia, Tourette's syndrome and obsessive-compulsive disorder.

Joseph Garner notes that abnormal repetitive behaviours in captive animals appear to involve the same mechanisms as abnormal repetitive behaviours in human psychiatry reflecting underlying abnormalities of brain function (Garner, 2005). Garner draws respective links between stereotypes, appropriateness, self-injury and deleterious outcomes, peculiarity and distress in animals with the psychiatric criteria 'violation of norms', 'unexpectedness', 'disability or dysfunction', 'statistical infrequency', and 'personal distress'. Garner and colleagues drew connections between the provision of an enriched environment and the reduction of stereotypes (Meehan, Garner & Mench, 2004).

The role of opiates in psychiatric illness is long established and well documented (Shah & Donald, 1982; Usdin, 2000). Hence the connection between the endogenous production of opiates with trauma and stress provides a well documented link between impoverishments of sociological/physical habitat and behaviours such as drug addiction (Volkow & Fowler, 2000), stereotyped behaviours, cognitive dysfunction and mental illness (Sinha, 2008).

## Drugs of Abuse Mechanism of Action Converges in the Opioid System

The opioid system and its biomarkers may be able to provide a prospective unifying framework to understand behaviours associated with problem drug use and wellbeing. Through such contextualised understandings this framework may be able to offer insights into more effective interventions in the case of over dose along with integrated understandings of statistical data sets associated with polypharmacy.

Alcohol acts through the hypothalamic-pituitary-adrenal (HPA) axis and the endogenous opioid system are activated in response to stress as well as after alcohol consumption (Gianoulakis, 1998). The effects of ethanol intoxication and withdrawal have been associated with dopamine which condenses with acetaldehyde, the primary metabolite of ethanol, to form tetrahydroisoquinolines (TIQs). Tetrahydroisoquinolines function as opioids (Bonner, Thomson, Cook, 2019).

Opioid peptides produced in the body act as neuromodulators that modify the actions of other neurotransmitters in the central nervous system. By activating the opioid peptide system alcohol contributes to alcohol reinforcement and excessive alcohol consumption. Agents that inhibit the opioid peptide system decrease alcohol self-administration in animals and reduce craving and alcohol consumption in human alcoholics (Froehlich, 1997).

The work of Sinclair (2001) examined the efficacy of using opiate blockers in supporting bringing about extinction behaviours in active alcoholism. This approach may have further application in addressing behaviours which relate to other drugs that operate through the same biochemistry (Noble, Lenoir, & Marie, 2015). In surveying clinical literature examining the mechanism(s) of action of a range of drugs with potentials for abuse it became apparent that a large range exhibit convergence in the physiology of opioidal biochemistry.

Alcohol (Singh, 2019; Olive, Koenig, Nannini, & Hodge, 2001), cannabis (Richards, Schandera & Elder, 2017), cocaine (Schroeder, Niculescu & Unterwald, 2002), methamphetamines (Tien & Ho, 2011; Colasantia et al, 2012), nicotine (Berrendero et al., 2010), caffeine (Kuribara & Uchihashi, 1994), and overt opiates all have their actions rooted in opioidal physiology. Psychiatric drugs also act through targeting the same physiology including benzodiazepines (Duka, Wüster, & Herz, 1979; Solhi et al., 2011), antipsychotics (Janssen, 1965; Downes, Lewis & Stone, 1986), lithium (Simantov, 1981) and tricyclic antidepressants (Pierluigi, Dedoni & Olianias, 2010).

## Conclusions:

The chief aim of this poster is to reveal the scope which such a framework has. The opioid system offers a potentially helpful framework in understanding interactions in polydrug use. Understanding drug use and behaviour through this perspective might offer up new therapeutic applications of long established medicines such as naloxone and naltrexone.

The potential of non opiate biomarkers such as prostaglandin E1 (Horrobin, 1978) and prolactin (Horrobin, 1973) may also offer potential for assessing where an individual is on an index of accumulated opioid interaction. This approach also suggests a nontoxic psychiatric intervention to work with trauma induced stress where the aim is to reduce abnormal repetitive behaviours, potentiate memory function and facilitate behaviour change.

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