

The promise of Opioid Receptor Antagonist drugs in the treatment of neuropsychiatric disorders

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Summary

The endogenous opioid system, either directly or through its influence on other neurotransmitter systems, has far-reaching effects on normal as well as abnormal (maladaptive) behaviours, thoughts and mood states. Altering this system through the use of an opioid antagonist medication may not only be useful in treating recognized psychiatric illnesses, but may also prove to be valuable in elucidating psychophysiological abnormalities that could contribute to the foundation of these disorders.

Opioid Antagonists Naltrexone and Naloxone have been used in substance abuse illnesses (narcotics, alcohol, tobacco) but have also been administered in variety of psychiatric conditions, including Anorexia Nervosa, Bulimia, Schizophrenia, Self-injurious Behaviour (as part of Borderline Personality Disorder and other conditions), Autism, Obsessive-Compulsive Disorder, Tourette's Disease and Trichotillomania.

A review of the clinical effectiveness of Naltrexone and Naloxone reveals many situations that call for a therapeutic trial on opioid antagonists in these conditions, despite the lack of a robust database demonstrating the clear efficacy of these medications in the global resolution of any of these conditions. A psychopathological reconceptualization of the conditions mentioned above, focusing on symptoms rather than syndromes, may prove to be of great clinical value.

Key words: Opioid Receptor Antagonists - Neuropsychiatric Disorder Treatment

Opioid Receptor Antagonists (ORAs) have been widely studied for use in various phases of the treatment of substance and alcohol abuse [3,4,5,7,8]. In addition, there is a growing body of evidence indicating the usefulness of this class of medications

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in non-opiate and non-substance abuse Neuropsychiatric disorders such as Obsessive-Compulsive Disorder, Eating Disorders, Autism, Schizophrenia, Borderline Personality Disorder (Self-Injurious Behaviour), Gille de la Tourette's Syndrome, and Trichotillomania.

In various countries around the world most current research and clinical usage has been accounted for primarily by three agents:

Naloxone, which has a very short elimination half-life, and is only available in injectable preparations.

Naltrexone, which has an elimination half-life two to four times longer than Naloxone, and is available in oral preparations.

Nalmefene, which has an elimination half-life similar to Naltrexone when given in oral form, and one of about ten hours after administration by injection.

There exists no comprehensive database supporting the use of any of the ORAs as monotherapy in the treatment of any of the above-mentioned neuropsychiatric conditions, but there does exist a rather broad database supporting the use of these agents as adjunctive agents in at least certain subsets of patients within these diagnostic categories. For discussion of this literature we refer the reader to the comprehensive review of this topic by Reneric and Bouvard [6].

The current system of Psychiatric Classifications now in use may not be optimally sensitive for purposes of noting true utility of certain novel pharmacological agents being employed in experimental paradigms or in novel clinical practices. That is because the ICD 9 and DSM IV Systems of Diagnosis conceptualize diseases as syndromes, which are aggregates of symptoms. If we look at all patients who might qualify for a given diagnosis, they would not all share common features of the disorder as a requisite to receive that diagnosis. It may very well be that certain pharmacological agents may be particularly effective in controlling certain symptoms perhaps present in some members, but not all in other members in a given diagnostic class. Some individuals with a given diagnosis may simply not have that targeted symptom. Any research study that merely analysed outcome globally on all members in a given diagnostic category can miss a positive effect in a significant subset of those patients with a given symptom sensitive to positive change from a pharmacological agent. An examination of the diagnostic criteria for Borderline Personality Disorder is instructive.

The DSM IV Diagnostic Criteria are:

301.83 Borderline Personality Disorder

A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

- (1) frantic efforts to avoid real or imagined abandonment. Note: Do not include suicidal or self-mutilating behaviour covered in Criterion 5*
- (2) a pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation*
- (3) identity disturbance: markedly and persistently unstable self-image or*

sense of self

(4) *impulsivity in a least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating). Note: Do not include suicidal or self-mutilating behaviour covered in Criterion*

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(5) *recurrent suicidal behaviour, gestures, or threats, or self-mutilating behaviour*

(6) *affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days)*

(7) *chronic feelings of emptiness*

(8) *inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights)*

(9) *transient, stress-related paranoid ideation or severe dissociative symptoms*

In order to receive a diagnosis of Borderline Personality Disorder one must meet five of nine criteria. This implies that there are thousands of permutations which could lead to a diagnosis of Borderline Personality Disorder. In a given study of BPD subjects having any given symptoms or set of symptoms may be over-represented or under-represented compared with other studies dependent on numerous factors. For example, subjects recruited from inpatient units may have an over representation of BPD patients who suffer from suicidal acts, self-mutilating behaviour or paranoid ideation, as these symptoms may be largely responsible for the patient being confined in hospital. Conversely, subjects recruited from a university-based student infirmary may set up a particularly strong bias against these symptoms, as a subject with BPD who suffered from these particular symptoms would be less likely to be enrolled as an active university student.

The testing of novel agents or the treatment of BPD may, therefore, be greatly influenced by the recruitment issues related to the cohort under investigation. There have been several studies supporting the use of Opioid Receptor Antagonists in treating Self-Injurious Behaviour. Self-Injurious Behaviour in BPD is distinguished from repetitive suicidal or parasuicidal behaviour in that the patient in question clearly reports that the intention of his or her activity is not to die; it is usually described as a method of reducing stress, self-calming or breaking a state of terror. Common behaviours include superficial cutting, burning, skin picking and head banging. Such descriptions, on what are, at first sight, phenomenological grounds seem to sum up cognitive states that are likely to be mediated at least in part by an endogenous opioid system.

So, if a clinician has a patient with Borderline Personality Disorder who displays Self-Injurious Behaviour in such a form that this symptom is of particular clinical significance, any intervention which aids in its control or elimination may be of great clinical benefit. This would be true regardless of whether other features of BPD in the given patient showed or did not show improvement. The lack of overall

global improvement in a patient, or the lack of improvement in most patients within a given diagnostic category, does not necessarily negate the potential strong benefit a given medication might bring or a particular patient might enjoy. Such may be the case in using the Opioid Receptor Antagonists in Self-Injurious Behaviour, when found as part of BPD or of other conditions, such as Autism or Mental Retardation.

It has been hypothesized that ORAs can block the euphorogenic or rewarding aspects of Self-Injurious Behaviours, which, over time, will lead to their extinction. Behaviours whose overall effect might have been pain-relieving may be experienced more as pain-engendering. The euphoria of a given act, now blocked, only leaves a residue of pain, anxiety or angst. Hopefully, psychotherapy and other interventions will then aid the patient to more adaptive patterns of behaviour.

Similar hypothesizing can be extended to other conditions such as Obsessive-compulsive Disorder. Obsessions are intrusive thoughts or emotional states that are experienced as intrusive and irrational, and that cause anxiety, discomfort or angst. Compulsions are behaviours or thoughts that neutralized, block or “break through” the obsessions or the state of discomfort they cause. Compulsions are often “done” in a stereotypic or ritualistic manner. Certain compulsions, when primarily associated with pleasure in and of themselves, may be referred to as “impulsive”; this is true of compulsive gambling, shopping or sexual activities.

ORAs have been employed as adjunctive medications for treating OCD. The mechanism of their benefit is unclear. One provocative hypothesis, which recapitulates on the above discussion related to Self-Injurious Behaviour, is that ORAs may interfere with the “euphorogenic” effect of compulsive/impulsive activities. In some forms of OCD, obsessions may be of primary clinical importance, whereas in other forms compulsions/impulses may be of primary clinical importance. As discussed above, there may be targeted subsets for which ORAs hold promise, even if they are not indicated globally for all patients who would qualify for a diagnosis of OCD under our current diagnostic systems. An obvious area for targeted research is that marked by “impulsivity”, a tendency that can lead to severe occupational, familial or social disability, such as that associated with compulsive/impulsive gambling, shopping or sexual activities.

There appears to be wide distribution of opioid receptors through the areas of the central nervous system involved in such functions as perception, mood and behaviours. In addition, the endogenous opioid system interacts directly or indirectly with all other major neurotransmitter systems known to be involved with the major neuropsychiatric diseases discussed above [1].

We need to humbly bear in mind that our current systems of classification are arbitrary; they do not constitute the only way to conceptualize manifest psychiatric disease. Our current systems of classification emphasize syndromes which are aggregates of symptoms, yet there may be symptoms which cut across many different disease categories that are more sensitive to treatment with given agents than the larger syndromes [2]

At present, data support trials of ORAs in selected subsets of patients suffering from a variety of neuropsychiatric conditions. Clinical trials focused on specific symptoms associated with particular distress or disability for a given patient may be more fruitful than those that investigate traditionally conceptualized syndromes or diseases.

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