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Use of tramadol in psychiatric care: a comprehensive review and report of two cases

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Summary

Tramadol is widely prescribed for treating acute and chronic forms of pain. It is a weak mu-receptor opioid agonist and also increases concentrations of serotonin and noradrenaline within the limbic system of the brain. The therapeutic range of tramadol is relatively wide. Compared with other opioid agonists, there is little risk for developing tolerance and for abuse. Recent models of depression emphasise the subjective experience of a depressive mood as being, in part, a psychologically painful state. It is well established that psychological stress due to social separation/loss, disruption or betrayal of pre-existent significant interpersonal bonds is mediated by the activation of the mammalian PANIC (separation-distress) system. It is also known that this kind of stress can be soothed very effectively by very low doses of endogenous or exogenous opioid receptor agonists. These observations raise the question of whether tramadol can be an effective and safe treatment option for some forms of anxiety and depression in which elements of social loss or betrayal are involved. In support of this possibility, two clinical cases are presented, and ideas for development of new approaches targeting the endogenous opioidergic system in clinical practice are discussed.

Key words: *tramadol; buprenorphine; opioids; depression; separation distress; SEEKING system; PANIC system; social attachment; drug development*

Introduction

Depression is the most common serious psychiatric disorder worldwide. In high-income countries about 14.6% of all individuals have presented a major depressive episode at least once in their lifetime [1]. This condition is also known to be very heterogeneous with regard to its neurobiological underpinnings, as well as to the specific strategies of treatment that might be most beneficial for its various forms. Thus, classification and treatment recommendations for depression are undergoing constant evolution and debate by clinicians and researchers [2].

One important aetiological factor in the development of a depressive episode is the occurrence of a severe external stressor, often in the social domain, that produces negative affect and challenges the individual's ability to cope with various forms of stress [3]. Persistence of the stressor often generates a cascade of adaptive mechanisms in the brain and body, which puts the individual at risk for developing chronic forms of depression and impaired stress responsiveness/resilience [4, 5]. More precisely, it has been shown that depression in patients with a history of interpersonal trauma responds to treatment strategies differently from depression that is devoid of traumatic aetiology: depressed patients with a history of interpersonal trauma commonly benefit more from psychotherapy than from psychopharmacotherapy [6].

For a long time, observable manifestations of depression such as lack of motivation or loss of vital energy, as well as feelings such as hopelessness and low self-esteem, have been a focus of clinical interest when developing classifications and treatment strategies for depression. However, the fact that depression can reflect a psychologically painful state from the patient's subjective perspective has recently been emphasised [7, 8]. There is a close relationship between the experience of psychic pain and the clinical manifestation of depression, and there is some evidence that pain and depression share common pathways within the brain [9].

Stress due to social disruption and loss are of particular interest when considering the impact of diverse stressors on mind and body. It is important to note that, in common language, very distressing feelings of suffering are often related to descriptions of physical pain (e.g., having a

"broken heart"). Thus, it was hypothesised that, in mammals, the structure and functioning of the physical pain system, was adapted in brain-mind evolution to promote social bonding [10–13]. Recently, endogenous opioids have been shown to regulate such social affective processes in humans and it is supposed that by reducing the potential harmful consequences of social rejection or exclusion [14, 15]. Furthermore, it has been confirmed that the perception of the pain of social loss is promoted by the same brain regions that mediate the perception of physical pain [16].

One of the most vivid and psychologically painful states known in mammals is called "separation distress". This psychological pain response can be observed in practically all infant mammals that are even briefly separated from their mothers – they promptly begin to cry. Such distress vocalisation in animals can be effectively soothed by the administration of very low doses of opioids that act on mu-opioid receptors [17], which are concentrated in the medial regions of the midbrain and thalamus [18]. This and other observations concerning opiate-mediated expression of both pleasure due to social reward and pain due to loss of social support have been conceptualised in the brain opioid hypothesis of social attachment [19]. In brief, this hypothesis states that the striving for and obtaining of close social bonding and support is one of the most important sources of social motivation and psychological well-being for mammals. This appetitive drive is processed through a brain motivational (appetitive exploration/enthusiasm) network called the SEEKING system, also commonly known as the brain reward system [10, 12, 20]. On the other hand, the loss of social proximity and support from peers is in general perceived as life-threatening. This perception activates a separation distress response that is mediated by another emotional system formally called the PANIC system (partly because this system may also promote panic attacks; for further relevant discussion of concepts and terminology see [11]). This model proposes that the negative affect of depression can often be explained by an imbalance within these two systems: a lack of motivational drive promoted by the SEEKING system, and excessive arousal of psychic pain promoted by the PANIC system. These two affective states can be present simultaneously and are extremely unpleasant for individuals experiencing them.

One psychiatric implication of this view of basic emotions is that sustained, psychologically painful suffering is a primal cause of clinical depression, which has been affirmed in animal models [21]. This has led to the idea of using low doses of opioid agonists for treating forms of depression that are characterised by a high intensity of psychological pain [7, 20].

This idea has a long history in psychiatry. Opioidergic medications, beginning with the opium-containing laudanum, then further developed with synthetically produced variants such as morphine and heroin, have been commonly used, since ancient times and until the middle of the last century, to soothe various forms of affective disorders, many of them corresponding to the psychosomatic complaints and depression of today's world [22, 23]. Eventually their use became restricted in most countries because of the high likelihood of addictive problems. However, the question of whether opiates might be useful for treating depression has continued to be discussed repeatedly in the past 50 years [22, 24–26].

It is known that opiates have a direct effect on depressed mood through direct actions on opioid mu-receptors [27, 28]. In addition, opiates may have an additional antidepressant effect by promoting serotonin release by neurones located in the raphe nucleus [29].

Buprenorphine is an opiate receptor partial agonist that is well established in the treatment of acute pain and opiate addiction because it is relatively safe since its effects on respiratory depression are modest compared with full mu-receptor agonists. It also blocks kappa-receptors which are widely recognised to promote negative affect. Clinical and preclinical data are converging to suggest that its use for treating depression is worth reconsidering [30–35]. However, in most countries the use of buprenorphine is highly regulated. Long-term prescription is only possible if approved by public health authorities. Thus, buprenorphine is unlikely to be accepted in the foreseeable future as an "off label" treatment for depression.

There are alternatives. For instance, tramadol is a synthetically produced, low potency opioid mu-receptor agonist, which is also known to be an inhibitor of the reuptake of the brain monoamines serotonin and noradrenaline. Tramadol is largely prescribed by general practitioners for the treatment of various forms of acute and chronic pain. Its prescription is not as restricted as the prescription of other opioid agonists, such as buprenorphine or oxycodone, and it does not have the reputation of a major substance of abuse, nor is it a desirable substitute for severe opioid drug addiction.

The idea of using tramadol as an antidepressant is not new as there are many animal studies that have demonstrated antidepressant effects [36–38]. Interestingly, there are currently no published randomised controlled trials comparing the efficacy of tramadol with standard antidepressants for treating depression. However, there are a few reports showing its beneficial effects in clinical settings, such as the treatment of refractory major depression [39], post-traumatic stress disorders (PTSD) [40] and severe suicidal ideation [41]. In summary, tramadol needs to be further evaluated for the treatment of depression, as it is short acting, has a large therapeutic range as a weak mu-receptor agonist, has a relatively low risk for inducing neurochemical tolerance, and comparatively low risk for abuse [42–45]. It has been found that tramadol was reported in only 1.5% of 16 775 investigations of prescription-drug diversion. The same study reported that benzodiazepines were involved in 28% of cases of prescription diversion, and hydrocodone and oxycodone, which are other frequently prescribed opiates, in 40% and 20%, respectively [46]. Despite its relatively low abuse

potential, tramadol was recently scheduled as a class IV substance in the USA and as a class C schedule 3 drug in the UK.

With regard to the most relevant side effects of tramadol, it is known to lower seizure thresholds, and therefore should not be taken by patients with a history of epilepsy [42]. Following intake of tramadol doses within or above the recommended daily dose range of up to 400 mg, the following intoxication effects have been noted: lethargy (30%), nausea (14%), tachycardia (13%), agitation (10%), seizures (8%), coma (5%), hypertension (5%) and respiratory depression (2%) [44]. However, it is important to note that most of the above side effects occurred while tramadol was taken concomitantly with other medications, drugs or alcohol.

There have been several reports that tramadol, especially when given in conjunction with selective serotonin reuptake inhibitor (SSRI) antidepressants, can contribute to the promotion of a "serotonin syndrome" and patients need to be informed and monitored regarding this potentially life-threatening complication [47]. As the metabolism of the main analgesic derivative of tramadol is catalysed by cytochrome P450 (CYP) 2D6, special attention has to be paid when tramadol is prescribed concomitantly with molecules that inhibit or increase activity of CYP2D6 [48]. Other relevant psychiatric complications related to the use of tramadol are the provocation of manic or psychotic episodes [49–52]. These complications can probably be best explained by the property of tramadol to inhibit synaptic re-uptake of brain monoamines.

Here we report two cases of psychiatric patients who, after having tried many of the typically prescribed medications for depression, wished to keep tramadol as their medication of choice. As the antidepressant effects of tramadol might be explained to a substantial extent by its opioid action to reduce psychological pain, especially of the kind related to social separation, this report emphasises the life histories of the treated patients, with special regard to their social attachments. The patients gave their informed consent to the publication of their case history. The descriptions are slightly modified in order to ensure anonymity.

Case 1

A 42-year-old man was followed-up in a psychiatrist's practice for depression. Besides depressive mood, he presented many PTSD-like symptoms such as frequent traumatic intrusions, hyperexcitability, hypervigilance, nightmares and insomnia. These symptoms arose as a result of a severe conflict at his workplace. Having recently been promoted into a leading position after ten years of employment, he suddenly found himself being massively bullied by his superior and a co-worker. In addition to this stressful situation at work, the man was going through a difficult divorce. His ex-wife was trying to withhold contact with the man's two young children, with whom he was very close. The man was in good health, practicing endurance sport on a regular basis. There was no significant psychiatric or somatic disease in his medical history. No abuse of alcohol or drugs was reported and the patient was not on any medication. Upon evaluation, a psychiatric medication was proposed, and the patient agreed to take escitalopram at a dosage of 5 mg/d. He noted a clear improvement of his mood, but decided to discontinue the antidepressant prescription after 4 months, wishing not to maintain a daily intake of a psychoactive substance. Bullying at the workplace persisted, as well as court trials concerning the custody of the patient's children. As a consequence, insomnia, traumatic intrusions and depressive mood continued to be the patient's main complaints. Additional treatment with zolpidem, oxazepam, hydroxyzine and quetiapine were introduced, all of which the patient agreed to take in an alternating way and only at night time when needed for sleep facilitation in dosages of 5 mg, 15 mg, 25 mg and 25 mg, respectively. While travelling abroad with his children, the patient suddenly developed severe back pain and was prescribed diclofenac tablets and tramadol aqueous solution during an emergency room visit, in order to control the pain and enable him to continue the journey. When taking tramadol, the patient noted not only a marked reduction of the pain, but also a clear improvement of his mood. Once the lower back pain completely resolved he continued to take tramadol occasionally to benefit from the mood elevating effect of this substance. After discussion with his treating psychiatrist, who was willing to maintain the tramadol prescription, the patient took 15 to 35 mg once or twice a day in accordance with his mood and the day's challenges (e.g., before going to child custody hearings); he took tramadol no more than three days in a row, nor more than five days per week. The mood elevating effect was noticeable after about one hour and lasted for approximately seven hours. For several months the patient continued to treat his depressive mood with tramadol on an "as needed" basis and no longer used the aforementioned sedating agents for insomnia. He was able to negotiate a transfer to another position within the same institution. He also maintained close contact and a good relationship with his children. In short, he was able to re-establish a stable and positive psychosocial environment.

Case 2

A 53-year-old woman had been in treatment with many healthcare professionals and institutions for many years because she suffered from recurrent depressive disorder and intermittent alcohol abuse. As a newborn she lost her family while living in a foreign country; she was brought to Switzerland at the age of two and raised in a foster family. During adolescence she endured long episodes of physical and sexual abuse and started excessive alcohol consumption at the age of 16. She was violently beaten by her husband and lost an eye when she was 33 years old. At various points most of the common antidepressants, such as escitalopram, venlafaxine, mirtazapine,

sertraline, fluoxetine, and trazodone were prescribed by treating psychiatrists. However, the patient did not experience a durable improvement of mood or functioning. Instead she suffered from severe oedema induced by these medications and had an increased incidence of suicidal thoughts. At the age of 49 years she had to undergo surgery and as a result received a tramadol prescription for pain control when leaving the hospital. In the subsequent weeks she realised that she felt a marked improvement of her mood after taking tramadol. She explained the effects of tramadol in the following way: "Tramadol helps me with addressing and soothing my suffering better than the antidepressants." In addition, she noticed that whilst taking tramadol regularly, she consumed significantly less alcohol. She therefore continued taking tramadol aqueous solution on a daily basis at a dosage ranging between 25 and 100 mg. Her psychiatrist agreed to renew the prescription. During the duration of treatment the patient never felt the need to increase the dosage beyond 100 mg/d and after 6 months of daily use she tapered off tramadol within 2 months. The patient reported she felt better in general and became abstinent of alcohol. Recently, the patient developed an intensive fear of the possible loss of contact with one of her two sons. Her son was having substantial difficulties completing a professional training course and was at risk of getting involved with "the wrong crowd". As a consequence of her constant worry, the patient relapsed into heavy alcohol consumption (up to two litres of wine per day) and reported increased need for psychiatric medication. She therefore agreed to take quetiapine 100 mg daily in addition to alprazolam (up to 2 mg daily, as needed) as prescribed by her psychiatrist. Remembering the beneficial effects of tramadol, the patient, in agreement with her doctor, reinitiated that medication and on the first day again experienced a marked decrease in depressive mood and her craving for alcohol. In the following months she maintained a daily use of tramadol, with dosages ranging between 50 and 100 mg, and continued to be abstinent from alcohol. When the worry for her son was reactivated by new incidents, she resumed a low quantity use of alcohol (two glasses of wine per day).

Discussion

These case studies are shared for practitioners within a translational perspective to consider the use of tramadol in cases of mild to moderate depression. The historical utility of opioids in treating depression, along with evidence stemming from many preclinical studies suggest that the use of relatively safe, low-acting opioids such as tramadol may be a useful strategy, especially when other treatments have failed.

In the two cases reported here the presence of severe interpersonal social stress is highlighted. The man described in case one endured two distinct types of social stress: first he faced sudden exclusion from his workplace, where he had been integrated and highly engaged for a long period of time; second, he was exposed to the danger of being separated from and losing the connection with his children. Thanks to his psychiatrist's supportive treatment, as well as to the various medications taken "as needed", the most relevant of them being tramadol, he was able to maintain a high level of functioning on both the social and the professional level. There were no relevant side effects and, importantly, there was no development of tramadol abuse.

Case number two is striking owing to the high degree of adverse events throughout the life of this woman. It is very likely that the loss of her biological family, the placements in foster homes, especially the abuse perpetrated by "caregivers" and eventually the violent aggression of her spouse (leading to the loss of an eye) contributed highly to the development of chronic depression and alcohol abuse. It is also interesting to note that the patient relapsed into a high level of alcohol consumption when she was afraid of losing contact and bonding with one of her sons. This kind of perceived loss appears to have the ability to stimulate an intense stress reaction, similar to the aforementioned "separation distress" (PANIC/separation-distress system response described in abundant aforementioned animal work). Eventually the patient resumed taking tramadol, and both her depressive mood and her excessive alcohol consumption improved within hours. This patient took tramadol on a sustained daily basis (with many months of follow-up), without ever increasing the dosage beyond 100 mg per day, and the beneficial effect on depressive mood and alcohol use was maintained at this low dosage level. This efficacy of tramadol for significantly reducing alcohol consumption may reflect its use as an appropriate pain medication for a patient whose alcohol abuse might be conceptualised as a chronic psychological pain disorder [53].

In both cases, tramadol promoted termination of intake of the previously used sedating medications (case one) and the excessive use of alcohol (case two). Thus, tramadol appears to be a beneficial medication for treating forms of depression in which factors of social stress due to interpersonal problems or disruption of significant bonding are evident and cannot be reduced in the short term by other interventions, such as psychotherapy.

It is somehow surprising that tramadol and other "safe" opioid agonists such as buprenorphine, are prescribed only marginally by psychiatrists and family doctors and typically only as the continuation of a treatment that was initiated for the management of physical pain. As such, the two cases reported here illustrate how tramadol was identified as an effective antidepressant treatment within a gradual process of testing out several alternative medications. Both patient and prescribing physician needed to have a high level of openness that allowed the recognition of the striking therapeutic effects of tramadol on the one hand, as well as the willingness to maintain its "off label" prescription, on the other hand.

Currently, tramadol as well as buprenorphine are pharmacologically well investigated and clinically well-established substances, which act on central opioid systems and are known to be comparatively safe with regard to

development of addictive urges and life-threatening intoxication, especially at the low doses that may be needed to treat depression (e.g., [31, 35]). Of course, prescribing physicians should remain alert to the possible emergence of a "serotonin syndrome" from overdoses of tramadol [47].

Whether the potentially unique effects of tramadol are due exclusively to gentle facilitation of opioid activity in the brain, or associated monoamine changes, or a mixture of the two, needs further investigation. Already in the mid-1990s there was a surge of interest in using buprenorphine for the treatment of refractory depression. Based on the review of case-studies by Bodkin et al. [31], as well as on his own clinical observations with patients for whom buprenorphine was found to be "dramatically effective", Callaway expressed concerns about the lack of interest by the manufacturer of the substance, by physicians and by the National Institute on Drug Abuse to develop buprenorphine as a treatment option for indications other than pain control or as a substitute for treating severe opiate addiction [54]. Meanwhile, buprenorphine has indeed become a well-established option for treating opiate addiction in many countries, but it is possible that this identity as a treatment of choice for severe drug addiction leads to a "stigmatisation" of this substance, and may hinder clinicians and regulatory authorities from giving a proper hearing to proposals for other possible useful indications. Such biases may be less onerous for tramadol.

Specifically, tramadol, which is not particularly involved in the field of addiction medicine, might be in a better position to gain the attention of the various players who are well placed to investigate whether a new indication for tramadol, such as depression, can be formally established. Another argument in favour of tramadol in the treatment of depression is the fact that it elevates monoamine levels in synaptic clefts, whereas buprenorphine does not have this ability. Thus, tramadol has a triple action (functional serotoninergic, noradrenergic and opioidergic agonism) all of which are relevant in treating psychic suffering, especially suffering from the feelings of psychic "pain" that can arise from social loss.

In summary, tramadol seems to be a useful option for treating acute psychiatric crises due to sudden affectively painful losses or disruption of social cohesion (e.g., rupture of relationships, death of loved ones, loss of the workplace, etc.). The short-term use of tramadol during such social crises would also diminish the risk that this medication might become a substance of abuse. If tramadol turns out to be an equally or, possibly, better option than the most commonly used antidepressants for managing chronic and treatment-refractory depression, long-term tramadol treatment might be a viable long-term prescription strategy as well, since, as discussed, there are few reported cases of rapid tolerance and escalation of doses. Thus, most patients might benefit from tramadol's effects without needing increases in dosage beyond the range known from well-established pain-control best practice.

With regard to the evident difficulties of basic neuroscience and of the drug industry to find and implement new molecules and strategies for treating depression [11, 12], it is obvious that additional efforts should be undertaken to evaluate treatment options focusing on the endogenous opioidergic systems of the brain, which are now well-established for controlling the psychological pain of social loss in animal models [7, 10]. Thus, further research should be undertaken to investigate the potential benefits, risks and side effects of tramadol use in future psychiatric care and to weigh the beneficial effects of tramadol treatment in comparison with the many long-established standard treatments.

However, there is a dilemma to be solved. For the past ten years there has been a dramatic rise in severe opiate addiction in North America, partly due to diverted medical prescriptions [55, 56]. Alarmed by this burden, practitioners may have overlooked relatively safe opioids, such as buprenorphine and tramadol. With our attention focused on the devastating aspects of opiate addiction, practitioners may also not be sufficiently aware of the possibility (which arises from the aforementioned vast literature describing the links between the endogenous opioidergic system and the evolutionary neurochemical coding of social reward/satisfaction in mammalian brains) that many people, in fact, are self-medicating with prescribed or nonprescribed opiates in order to reduce suffering from separation distress – the psychic pain that arises from social exclusion.

In accordance with this view, prescription of relatively safe opioid molecules could be considered an appropriate pharmacological manoeuvre to promote the emotional resources that all human beings need in order to thrive psychologically. When normal capacities to cope with psychological pain are severely compromised, tramadol used judiciously could be a "life saver".

Perhaps such approaches are not being adequately considered, since opioids have been culturally demonised, even though brain science has clarified how important our endogenous brain opioids are in naturally facilitating positive mood and happiness and in counteracting the diverse psychological-social "pains" that promote depression. More extensive well-controlled psychiatric research with such agents might help reverse such biases (for example [20, 35, 57]), and restore the use of safe variants of such agents to psychiatric practice. This may be especially important when more traditionally accepted approaches have failed to reverse the underlying anhedonia. As shown, safe opioids appear to be capable of soothing the most evident psychologically "painful" suffering that arises from the separation distress, and perhaps various other intrinsic negative affect systems of the brain.

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