Naltrexone Implant for Opioid Use Disorder

Subjects: Substance Abuse

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The research into therapeutic options for the treatment of opioid use disorder (OUD) has been long underway, beginning with the introduction of methadone in the 1960s. The approval of more drugs indicated in the treatment for OUD including buprenorphine and naltrexone has been and will continue to be crucial in combating the opioid epidemic.

Opioid Use Disorder | Opioid | Naltrexone Implant

1. Current Treatment of Opioid Use Disorder (OUD)

OUD treatment is aimed at reducing opioid withdrawal symptoms (OWS), preventing relapse, and reversal of overdose [1]. OWS includes hyperalgesia, tremor, anxiety, depression, intense cravings, irritability, nausea, vomiting, diarrhea, insomnia, lacrimation, sweating, and rhinorrhea among many others. These symptoms stem from adaptations that occur related to the routine use of opioid medications. The mesolimbic system has been associated with the intense cravings, depression, and irritability seen in OWS [1]. Nausea, vomiting, and diarrhea are associated with mu-opioid receptors in the GI tract. Many of the physically dependence symptoms seen in OWS haves been tied to the locus coeruleus (LC) and its projections [2]. Opioid binding to mu receptors on LC neurons causes a decreased firing rate which results in decreased respiration, muscle tone, blood pressure, and drowsiness. Continuous inhibition of LC neurons results in an adaptive response to increase baseline activity that offsets opioid effects and causes OWS in the absence of opioids [2].

The initial step in treatment for both discontinuation and the reduction in opioid dosing is management of OWS. OWS is managed based on the severity of a patient's OUD, which is determined by guidelines established in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* [1]. Management of OWS is performed medically. Opioid agonist therapy (OAT) is the preferred treatment for patients with moderate or severe OUD to alleviate OWS [3]. Methadone and buprenorphine are used for OAT. They are ideally started at the beginning of OWS and either kept at a low steady state or slowly tapered down over time. Methadone is a synthetic mu-opioid receptor agonist with a half-life of 28 h allowing for daily dosing [4]. Methadone reverses OWS by activating mu-opioid receptors, it decreases cravings for opioids and binds more avidly to the mu-receptors than used opioids which decreases their euphoric effects. Unlike abused opioids, methadone does not develop tolerance commonly and can be kept at a steady state for long-term management of OUD [5]. Buprenorphine is a semi-synthetic mu-opioid partial agonist and has weak partial agonist effects at the delta and kappa opioid receptors. If a patient takes buprenorphine shortly after using an opioid it will induce OWS. For this reason, patients should not use any opioid 12–24 h before taking buprenorphine [4]. Naltrexone is another medication that is used to prevent relapse in patients with OUD. Naltrexone is a mu-opioid receptor antagonist. This medication works by blocking the euphoria of opioids by binding and blocking the mu-receptor with a higher affinity [4]. Some patients with OUD might have contraindications to the use of OAT. Examples of these contraindications are mild OUD, patients who plan to be treated with naltrexone, and patients who desire opioid-free therapy [4]. For patients at the minimal dosage of OAT or who are contraindicated to start OAT, several nonopioid medications can be used to alleviate their symptoms. Lofexidine is an α-2 adrenergic agonist that is FDA approved for the treatment of OWS. α-2 adrenergic agonists alleviate many symptoms of OWS by acting as autoreceptor feedback inhibition on the LC pathways that cause noradrenergic hyperactivity [6]. Clonidine is another α-2 adrenergic agonist that has shown effective management of OWS that is comparable to lofexidine [7]. A number of techniques have been described and utilized successfully over the past two decades that employ clonidine, propofol, intubation, naloxone, and post-operative oral naltrexone to ultra-rapidly precipitate withdrawal under general anesthesia [8][9][10][11][12].

Other medications that are not FDA approved for the management of OWS have been used to alleviate more specific symptoms of OWS. Some examples include over-the-counter medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, which can be used for hyperalgesia and musculoskeletal pain. Ondansetron, prochlorperazine, and metoclopramide are medications that can be used for nausea and vomiting. Bismuth can be used for diarrhea associated with OWS. Eszopiclone, zolpidem, or low doses of trazodone and doxepin can be used for insomnia [1]. Loperamide and Benzodiazepines have been used in the past for the management of diarrhea and anxiety, respectively; however, these medications have a risk for abuse in patients with OUD and should be used with caution [13].

Patients who present with opioid overdose are in need of emergency treatment due to life-threatening respiratory depression. Naloxone is the drug of choice for emergent reversal of opioid effects and is a mu-opioid receptor antagonist. It displaces opioids off the mu receptor for rapid reversal of opioid overdose. Naloxone also causes rapid OWS due to displacement from the mu receptor. Patients should be treated with nonopioid medications such as another α-2 adrenergic agonist to alleviate these symptoms [1].

2. Naltrexone Implant

Since FDA approval in 1984, the use of naltrexone in tablet form has helped shape the treatment of OUD [14]. The approval of oral naltrexone initially showed much promise, as the drug was observed to be highly potent in antagonizing the effects of opioids while producing no opioid agonist effects of its own and having a favorable side effect profile [15]. However, like many of the other oral formulations available for the treatment of OUDs, treatment success is strongly correlated with patient compliance, making daily oral formulations a hit or miss strategy. This led to the research and creation of sustained-release forms of naltrexone to increase compliance and ultimately improve the overall effectiveness of the treatment. In 2010, the FDA approved a monthly depot injection of naltrexone for relapse prevention of both OUD and alcohol use disorder (AUD) [16]. Despite the fact this sustained-release depot formulation decreases the need for patients to take a daily oral medication, its efficacy still relies on patients returning once a month for repeat injections, making treatment with even longer-acting formulations a more desirable alternative [17].

Although not yet FDA approved in the United States, the efficacy and safety of naltrexone implants are being studied in Australia and various parts of Europe [18]. Many of the implants being studied have varying degrees of duration but could be efficacious for up to 6 months, dramatically reducing the need for continued daily or monthly compliance [17]. A naltrexone implant manufactured in Australia was implanted subcutaneously into the abdomen under local anesthetic and was designed to release a total of 2.3 g of naltrexone [17]. Researchers found that this dosing was able to maintain naltrexone levels at or above 2 ng/mL for approximately 5.5 months when standardized to a 70 kg person [17][19]. Further research is needed to examine the safety and efficacy of these implants, but current studies show that it may be a promising option in the treatment of OUDs moving forward.

Mechanism of Action

Naltrexone is a competitive inverse agonist of opioid receptors in the central nervous system (CNS), with the highest affinity for the mu-opioid receptor [20]. As an inverse agonist, Naltrexone binds to the same receptor-binding site as opioid agonists and antagonizes the effects of that agonist as well as exerts the opposite effect by suppressing the receptor signaling that would occur with the binding of an agonist [21]. Naltrexone may also reverse, although not fully, the effects induced by partial agonists. It is a cyclopropyl derivative of oxymorphone with a structure similar to naloxone and nalorphine [22]. Naltrexone has few intrinsic actions other than its blockage of mu-opioid receptors; however, it has been shown to produce pupillary constriction by an unknown mechanism [23]. By competitively occupying opioid receptors within the central nervous system, naltrexone may block the effects of endogenous opioid peptides [24]. The mechanism in which naltrexone is useful in the treatment of AUD is not fully understood, but it is believed to have to do with the blockage of endogenous opioids [20]. Naltrexone may also modify the hypothalamic–pituitary–adrenal axis, aiding in the suppression of alcohol consumption [25]. The competitive inhibition of the mu-opioid receptors leads to antagonization of many of the subjective and objective effects that opioids produce including respiratory depression, euphoria, drug craving, and miosis [26]. Inhibition of opioid receptors by naltrexone can potentially be surmounted by the administration of opioids and may lead to non-opioid receptor-mediated effects such as histamine release [20]. The use of naltrexone is not associated with the development of dependence or tolerance, and it has few side effects even when taken for extended periods [15]. Naltrexone has an overall favorable side effect profile; however, it does have a black box warning for causing hepatotoxicity when given in excess doses and therefore is contraindicated in patients with acute hepatitis or liver failure [27].

3. Safety and Efficacy

3.1. Safety

Naltrexone has a well-established safety profile [4]. It has some minor side effects such as headache, nausea, vomiting, and dysphoria, and these symptoms are typically not severe enough to stop the medication [28]. There is one black box warning for naltrexone which is hepatotoxicity [29]. The prevalence of the side effect among patients has a wide variance in different studies [29][30]. The most common lab abnormality seen in AUD is elevated liver enzymes due to the toxic effects of ethanol on

the liver [29]. Patients with a history of alcohol abuse or other causes of liver damage need to be assessed before starting naltrexone [29]. Patients with mild to moderate cirrhosis or chronic hepatitis can take naltrexone safely with routine monitoring [31]. Patients with severe cirrhosis, acute liver injury, or acute hepatitis are contraindicated from starting the medication [29]. In patients that are physically dependent on opioids, naltrexone use will precipitate withdrawal symptoms, and therefore it should not be used prior to the completion of a medically supervised withdrawal from opioids [32]. For this reason, naltrexone is contraindicated in patients taking buprenorphine, methadone, or any other opioid for medical purposes because it will negate the effects of the opioid agonists [33]. It may precipitate opioid withdrawal symptoms in a patient who has recently used an opioid agonist [4]. While OWS is not lethal on their own, acute exacerbations of OWS can be life-threatening due to volume depletion from vomiting and diarrhea [1]. For this reason, it is important to abstain from opioid use before beginning naltrexone therapy. Studies have shown that if a patient has used heroin or any other opioid within the last 7–10 days, they should not be started on naltrexone therapy [33]. If a patient is given naltrexone too soon and severe OWS are precipitated, they can be managed with buprenorphine, α-2 adrenergic agonists, or other medications targeted at specific symptoms [34].

3.2. Efficacy

Naltrexone has been proven to effectively block opioid receptors from being stimulated and prevent patients with OUD from experiencing the typical symptoms of using an opioid [4]. This makes it very useful in managing patients with OUD by completely blocking the effects of heroin or other abused opioids making relapse to other opiates very unlikely. The benefit of the medication can be considered two-fold causing positive reinforcement against the use of opioids due to negative reinforcement from monetary loss with no gain [35]. Patients that routinely take their naltrexone reported fewer days of heroin use and had more negative drug tests than those without treatment [36]. The challenge with oral naltrexone therapy, as stated earlier in this manuscript, is that it requires daily compliance. Many patients that struggle with OUD will abstain from their naltrexone use to use opioids again [17]. Naltrexone does not produce any adverse effects when it is stopped and does not relieve OWS when it is initiated so it is very easy for a patient with OUD to stop using the medication [37]. Unlike naltrexone, methadone and buprenorphine do have adverse events when stopped and relieve OWS when taken, therefore compliance is improved [37]. Treatment adherence has been historically poor for oral naltrexone, some studies have shown a retention rate lower than 20% at 6 months. A meta-analysis performed in 2011 showed that oral naltrexone therapy was no better than placebo treatment [38]. This is particularly concerning because opioid tolerance is reduced over time while a patient is on naltrexone, if a patient stops taking their naltrexone and abuses heroin or another opioid they are at an increased risk for overdose, respiratory depression, and death [39]. As with most medications used in treating addiction, naltrexone studies show that patient outcomes improve with social support, after-care counseling, compliance strategy training, and psychotherapy [37]. This shows that while naltrexone can be effective in the treatment process for OUD it should not be used alone without proper social structuring for the patient and any measures that can be taken to increase compliance will benefit the patient.

Poor outcomes in OUD patients treated with naltrexone have been directly tied to short treatment time, studies have proven that when patients are in treatment for long periods with naltrexone, they have variable outcomes [37]. A solution to the low compliance of oral naltrexone is the use of a sustained-release solution that is either injected or surgically implanted. Sustained-release preparations contain either compressed naltrexone or a naltrexone/polymer/copolymer combination [40].

A study in 2004 that measured the blood levels of naltrexone after the use of the 1.7 g and 3.4 g naltrexone injectable has shown that the injectable can maintain above therapeutic levels for 3 and 6 months, respectively [39]. This is beneficial for the patient because they do not have to be taken daily oral medications, which eases their path to recovery [37]. One study measuring outcomes of naltrexone given orally vs. as an implant at the 6 month interval showed a higher non-compliance rate among those who used oral medications at the 6 month mark [17]. It also showed that patients who used oral naltrexone returned to heroin use sooner than those that had used the implant (median [SE],115 [12.0] days vs. 158 [9.4] days) [17]. This shows a clear benefit of injectable naltrexone over oral. There seems to be a direct relationship between compliance and the length of time that the naltrexone injectable maintains therapeutic levels [17].

Another study performed in 2005 that measured outcomes at 12 months showed a statistically significant improvement in patient outcomes in patients using implants vs. taking oral medications [30]. Interestingly, it also showed proof that the longer a patient is on the naltrexone medication that their long-term outcomes will be better. For example, patients in the oral group who did not have a relapse had taken naltrexone for an average of 4 months during the study. Those who did have a relapse in the oral group had stopped taking their medicine on average within the first two weeks of the study [30]. The study also showed that patients' understanding of their medication affects outcomes. Of those in the subcutaneous injection group, the patients who did not relapse within the 12 month window believed the implant lasted longer, upwards of 6 months than those who did relapse which believed the implant only was effective for 3 to four months [30]. The 12 month study also showed data

on the effects of oral vs. implanted naltrexone on self-confidence at the 6 and 12 month mark. It showed that before treatment there was no statistical difference in patient's self-confidence levels, but there was a statistically significant increase in self-confidence in patients in the oral group at 6 months. Interestingly, there was no significant difference at the 12 month mark between the two. The study indicated that the improved self-esteem was maintained in the oral group, but the implant group rose to a similar level by the 12 month interval [30].

A study was performed in Australia measured the efficacy of oral naltrexone vs. an implant, but it focused more on blood levels of the medication and cravings for heroin or other abused opioids [40]. The study showed that blood naltrexone concentrations below 0.5 ng/mL were associated with a much higher risk of increased use of heroin and sensation of withdrawals. The study showed that at a concentration of 1 ng/mL of naltrexone patients had a 35% reduction in the odds of them using heroin. Patients with a blood naltrexone concentration of 3 ng/mL were associated with a very low risk of relapse; however, at dosages higher than 3 ng/mL there was no statistical evidence of increased effectiveness of naltrexone's ability to reduce cravings and prevent relapse [40]. The study showed that the patients that received the implanted naltrexone had a lower number of cravings for heroin and with it a lower rate of relapse. The implant group had one-fifth the risk of using heroin when compared to the oral group in this study [40]. One variance between the two groups that was interesting was that there were statistically significant lower cravings in the implant group with larger dosages of naltrexone, up to 3 ng/mL [40]. The oral naltrexone group had different results which showed no relationship between increased blood levels of naltrexone changing the amount cravings for heroin. The study concluded that an appropriate blood level for naltrexone for the treatment of OUD is 1 to 3 ng/mL, any treatment bellow 0.5 ng/mL is insufficient for treatment, and that implanted naltrexone might be more efficacious than oral naltrexone since it reduces non-compliance, as well as keeping a more consistent blood level of the medication for an extended period of time which appears to have effects on patient's cravings [40]. Another assessment made by the study is that there is a strong association between the intensity of cravings a patient has and imminent relapse. The study suggested screening for the severity of cravings could be used to determine if a patient needs more acute management of their OUD to prevent relapse in the near future.

Another aspect of naltrexone's efficacy and safety that has been studied is its effect on mental health. This is particularly important in treatment for patients with OUD because they have an increased rate of depression, suicidal ideation, and anxiety [41]. There were concerns that naltrexone could worsen negative symptoms seen in OUD due to the blockade of endogenous opioids that are important for pleasurable stimuli [41]. One study followed a group of patients with OUD and measured their anxiety, depression, and anhedonia before and after treatment with naltrexone. The study showed that patients with OUD had higher baseline levels of anxiety, depression, and anhedonia when compared to the general public, but it decreased back down to normal levels 1–2 months into treatment with naltrexone. This showed the opposite of what some had predicted would be a problem with naltrexone therapy.

Another study evaluated the number of hospital events patients had pre- and post-treatment with naltrexone implants to see if there is any correlation between the implant and mental health outcomes [42]. The research showed that there was not an increased rate of mental health-related hospitalizations in patients who were treated with naltrexone [19]. There was a significant reduction in the number of hospitalizations for non-substance mental disorders, substance-related mental disorders, and all-cause mental disorders in patients when compared pre- and post-treatment groups. Further stratification showed that this decrease in mental disorder-related hospitalizations was most prevalent in the male population of patients studied and was often nonsignificant in the female population [19]. There was a category of mental disorder that had no significant difference between pre- and post-treatment, regardless of sex, which was mood-related disorders. The study concluded that there was no increased risk for mental health-related incidents in patients taking naltrexone via a long-acting implant. Something the study did bring to light was in all the subgroups studied, young females with a history of mental illness had the highest rate of future mental illness-related events and would be considered a "high risk" group when treating OUD with naltrexone. Another observation made by this study was an increased risk for patients to have mental health problems in the future based on how long a patient has been using heroin and how much they had been using [42].

While there is a statistically significant improvement in compliance, it is still problematic with the injectable form. Reducing the number of times a patient has to take their medication will help increase their chances of achieving long-term sobriety goals, but only to a certain degree. A 2006 study showed that 30–40% of patients on the long-acting injectable of naltrexone failed to return for follow-up dosing [43].

References

1. Kosten, T.R.; Baxter, L.E. Review article: Effective management of opioid withdrawal symptoms: A gateway to opioid dependence treatment. In American Journal on Addictions; Wiley Blackwell: Hoboken, NJ, USA, 2019; Volume 28, pp. 55–62.
2. Kosten, T.R.; George, T.P. The neurobiology of opioid dependence: Implications for treatment. Science & practice perspectives/a publication of the National Institute on Drug Abuse, National Institutes of Health. Sci. Pract. Perspect 2002, 1, 13–20.
3. Abuse, S.; Health Services Administration M. Medications for Opioid Use Disorder TIP 63 TREATMENT IMPROVEMENT PROTOCOL For Healthcare and Addiction Professionals, Policymakers, Patients, and Families. Available online: https://www.surveymonkey.com/r/KAPPFS (accessed on 23 December 2020).
4. Bart, G. Maintenance medication for opiate addiction: The foundation of recovery. J. Addict. Dis. 2012, 31, 207–225.
5. Davis, A.; Inturrisi, C. d-Methadone Blocks Morphine Tolerance andN-Methyl-d-Aspartate-Induced Hyperalgesia | Journal of Pharmacology and Experimental Therapeutics. J. Pharmacol. Exp. Ther. 1999, 289, 1048–1053.
6. Ayanga, D.; Shorter, D.; Kosten, T.R. Update on pharmacotherapy for treatment of opioid use disorder. In Expert Opinion on Pharmacotherapy; Taylor and Francis Ltd.: Abingdon, UK, 2016; Volume 17, pp. 2307–2318.
7. Gowing, L.; Farrell, M.; Ali, R.; White, J.M. Alpha2-adrenergic agonists for the management of opioid withdrawal. In Cochrane Database of Systematic Reviews; John Wiley and Sons Ltd.: Hoboken, NJ, USA, 2009.
8. Kaye, A.D.; Banister, R.E.; Hoover, J.M.; Baluch, A.R.; Jacobs, S.; Shah, R.V. Chronic pain and ultrarapid opioid detoxification. Pain Pract. 2005, 5, 33–42.
9. Kaye, A.D.; Kaye, A.M.; Urman, R.D. Essentials of pharmacology for anesthesia, pain medicine, and critical care. In Essentials of Pharmacology for Anesthesia, Pain Medicine, and Critical Care; Springer: New York, NY, USA, 2015; pp. 1–904.
10. Kaye, A.D.; Gevirtz, C.; Bosscher, H.A.; Duke, J.B.; Frost, E.A.; Richards, T.A.; Fields, A.M. Ultrarapid opiate detoxification: A review. Can. J. Anesth. Can. Anaesth. Soc. 2003, 50, 663–671.
11. Urman, W.; Gross, B.; Gevirtz, C.; Frost, E.; Kaye, A.D. Opiate Detoxification (Ultra Rapid Detoxification), an Update. In Anesthesia Outside of the Operating Room; Oxford Press: Oxford, UK, 2018.
12. Kaye, A.; Gevirtz, C.; Bosscher, H.; Duke, J.; Richards, T.; Fields, A. A Complete Review of Ultra Rapid Opiate Detoxification. Can. J. Anaesth. 2003, 50, 663–671.
13. Sigmon, S.C.; Bisaga, A.; Nunes, E.V.; O'Connor, P.G.; Kosten, T.; Woody, G. Opioid detoxification and naltrexone induction strategies: Recommendations for clinical practice. Am. J. Drug Alcohol Abus. 2012, 38, 187–199.
14. Naltrexone Implant and How It Releases Medication into the Body. Available online: https://medlibrary.org/lib/rx/meds/naltrexone/ (accessed on 10 November 2020).
15. Comer, S.D.; Collins, E.D.; Kleber, H.D.; Nuwayser, E.S.; Kerrigan, J.H.; Fischman, M.W. Depot naltrexone: Long-lasting antagonism of the effects of heroin in humans. Psychopharmacology 2002, 159, 351–360.
16. Skolnick, P. The Opioid Epidemic: Crisis and Solutions. In Annual Review of Pharmacology and Toxicology; Annual Reviews Inc.: Palo Alto, CA, USA, 2018; Volume 58, pp. 143–159.
17. Hulse, G.K.; Morris, N.; Arnold-Reed, D.; Tait, R.J. Improving clinical outcomes in treating heroin dependence: Randomized, controlled trial of oral or implant naltrexone. Arch Gen Psychiatry 2009, 66, 1108–1115.
18. Naltrexone Implant Treatment for Alcohol and Opioid Addiction. Available online: https://rightpathaddictioncenters.com/naltrexone-implant/ (accessed on 10 November 2020).
19. Ngo, H.T.T.; Arnold-Reed, D.E.; Hansson, R.C.; Tait, R.J.; Hulse, G.K. Blood naltrexone levels over time following naltrexone implant. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 2008, 32, 23–28.

20. Naltrexone. DrugBank Online. Available online: https://go.drugbank.com/drugs/DB00704 (accessed on 5 November 2020).
21. Naltrexone (Complete Pharmacy and Medical Solutions): FDA Package Insert. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/018932s017lbl.pdf (accessed on 7 November 2020).
22. Naltrexone: Drug information-UpToDate. Available online: https://www.uptodate.com/contents/naltrexone-drug-information?search=naltrexone&source=panel_search_result&selectedTitle=1~98&usage_type=panel&kp_tab=drug_general&display_rank=1 (accessed on 7 November 2020).
23. Naltrexone-Side effects. Available online: https://reference.medscape.com/drug/vivitrol-revia-naltrexone-343333 (accessed on 6 November 2020).
24. DailyMed-NALTREXONE Implant. Available online: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=40b16844-bc1c-485e-aad3-2cb86e2eb009 (accessed on 20 November 2020).
25. Williams, K.L.; Broadbear, J.H.; Woods, J.H. Noncontingent and Response-Contingent Intravenous Ethanol Attenuates the Effect of Naltrexone on Hypothalamic-Pituitary-Adrenal Activity in Rhesus Monkeys. Alcohol. Clin. Exp. Res. 2004, 28, 566–571.
26. Naltrexone Black Box Warning|SinclairMethod.Org. Available online: https://www.sinclairmethod.org/naltrexone-black-box-warning/#:~:text=Naltrexone%20does%20not%20appear%20to,experience%20symptoms%20of%20acute%20hepatitis. (accessed on 5 November 2020).
27. Pharmacotherapy for Opioid Use Disorder-UpToDate. Available online: https://www.uptodate.com/contents/pharmacotherapy-for-opioid-use-disorder?search=Pharmacotherapy%20for%20Opioid%20use%20Disorder&source=search_result&selectedTitle=1~150&usage_type=defaul (accessed on 10 November 2020).
28. Bitri, S.T.; Puca, E.; Sotiri, E.; Thoma, E.; Puca, E. Liver Toxicity of Naltrexone. A Case Study and Review of Literature. 2018. Available online: http://medcraveonline.com (accessed on 23 December 2020).
29. Yen, M.H.; Ko, H.C.; Tang, F.I.; Lu, R.B.; Hong, J.S. Study of hepatotoxicity of naltrexone in the treatment of alcoholism. Alcohol 2006, 38, 117–120.
30. Mitchell, M.C.; Memisoglu, A.; Silverman, B.L. Hepatic safety of injectable extended-release naltrexone in patients with chronic hepatitis C and HIV infection. J. Stud. Alcohol Drugs 2012, 73, 991–997.
31. Iovcheva, M.; Zlateva, S.; Asparuhova, M. Precipitated Withdrawal Reaction to Opiates in Cases of Improper Use of Naltrexone. 2007, Volume 13. Available online: http://www.journal-imab-bg.org (accessed on 23 December 2020).
32. Kunøe, N.; Lobmaier, P.; Ngo, H.; Hulse, G. Injectable and implantable sustained-release naltrexone in the treatment of opioid addiction. Br. J. Clin. Pharmacol. 2014, 77, 264–271.
33. Boyce, S.H.; Armstrong, P.A.R.; Stevenson, J. Effect of innappropriate naltrexone use in a heroin misuser. Emerg. Med. J. 2003, 20, 381–382.
34. Colquhoun, R.; Tan, D.Y.K.; Hull, S. A comparison of oral and implant naltrexone outcomes at 12 months. J. Opioid Manag. 2005, 1, 249–256.
35. O'brien, C.P.; Greenstein, R.A.; Mintz, J.; Woody, G.E. Clinical experience with naltrexone. Am. J. Drug Alcohol Abus. 1975, 2, 365–377.
36. Minozzi, S.; Amato, L.; Vecchi, S.; Davoli, M.; Kirchmayer, U.; Verster, A. Oral naltrexone maintenance treatment for opioid dependence. In Cochrane Database of Systematic Reviews; John Wiley & Sons, Ltd.: Hoboken, NJ, USA, 2011.
37. Caplehorn, J.R.M.; Dalton, M.S.Y.N.; Haldar, F.; Petrenas, A.M.; Nisbet, J.G. Methadone maintenance and addicts' risk of fatal heroin overdose. Subst. Use Misuse 1996, 31, 177–196.
38. Comer, S.D.; Sullivan, M.A.; Hulse, G.K. Sustained-release naltrexone: Novel treatment for opioid dependence. Expert Opin. Investig. Drugs 2007, 16, 1285–1294.

39. Hulse, G.K.; Arnold-Reed, D.E.; O'Neil, G.; Chan, C.T.; Hansson, R.; O'Neil, P. Blood naltrexone and 6-β-naltrexol levels following naltrexone implant: Comparing two naltrexone implants. Addict. Biol. 2004, 9, 59–65.
40. Hulse, G.K.; Ngo, H.T.T.; Tait, R.J. Risk factors for craving and relapse in heroin users treated with oral or implant naltrexone. Biol. Psychiatry 2010, 68, 296–302.
41. Krupitsky, E.; Zvartau, E.; Blokhina, E.; Verbitskaya, E.; Wahlgren, V.; Tsoy-Podosenin, M.; Bushara, N.; Burakov, A.; Masalov, D.; Romanova, T.; et al. Anhedonia, depression, anxiety, and craving in opiate dependent patients stabilized on oral naltrexone or an extended release naltrexone implant. Am. J. Drug Alcohol Abus. 2016, 42, 614–620.
42. Ngo, H.T.T.; Tait, R.J.; Arnold-Reed, D.E.; Hulse, G.K. Mental health outcomes following naltrexone implant treatment for heroin-dependence. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 2007, 31, 605–612.
43. Comer, S.D.; Sullivan, M.A.; Yu, E.; Rothenberg, J.L.; Kleber, H.D.; Kampman, K.; Dackis, C.; O'Brien, C.P. Injectable, sustained-release naltrexone for the treatment of opioid dependence: A randomized, placebo-controlled trial. Arch. Gen. Psychiatry 2006, 63, 210–218.