ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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Comparative Evaluation of Naltrexone Implants Placed in Different Anatomical Regions According to the Suitability for Opioid Treatment and Wound Placement: A Plastic Surgery Perspective

Farklı Anatomik Bölgelere Yerleştirilmiş Naltrekson İmplantların Opioid Tedavisine Uygunluk ve Yara Yerleşimine Göre Karşılaştırmalı Değerlendirilmesi: Plastik Cerrah Perspektifi

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ABSTRACT Objective: Today, increasing opioid substance addiction has made implantation of subcutaneous opioid antagonists (such as naltrexone) a more popular treatment modality. In the literature, although the abdominal region is generally preferred for implantation, there is no study on the ideal location of these implants. In our study, it was aimed to evaluate and compare which of the dorsal or abdominal regions is the more ideal site for implantation, treatment compliance, surgical wound site and complications in these patient groups. **Material and Methods:** For this purpose, 181 patients who were referred to us by the psychiatry department in our clinic for subcutaneous implant placement for the treatment of opioid addiction between 2016 and 2019 were included in the study. Demographic characteristics, how many times and in which areas implantation was performed, whether the patients discontinued the treatment, if they did, the reasons for discontinuation, presence of signs of infection, implant extrusion, and secondary interventions were examined. **Results:** Subcutaneous naltrexone implant was placed in the back region in 95 patients and in the abdominal region in 86 patients. Based on the area where the implants were placed, the patients were evaluated in terms of parameters such as compliance to treatment, infection, secondary procedure requirement, and implant extrusion in the postoperative period. It was determined that patients with implants in the back area adapted better to the treatment, required fewer secondary procedures, and experienced less infection and implant extrusion. **Conclusion:** In the light of these findings, in cases where subcutaneous implantation is planned for the treatment of opioid addiction, the back region is a more ideal area for implantation compared to the abdominal region.

Keywords: Drug implants; naltrexone; opioid-related disorders; wound infection

ÖZET Amaç: Günümüzde, dünya genelinde artan opioid madde bağımlılığı, beraberinde cilt altı opioid antagonistlerinin de (naltrekson) implantasyonunu daha popüler bir tedavi seçeneği hâline getirmiştir. Literatürde, implantasyon için genellikle abdominal bölge tercih edilmesine rağmen bu implantların ideal yerleşim yeri ile ilgili bir çalışma bulunmamaktadır. Çalışmamızda bu hasta gruplarında sırt veya abdominal bölgeden hangisinin implantasyon için daha ideal bir alan olduğu, tedavi uyumu, cerrahi yara yeri ve komplikasyonların değerlendirilerek karşılaştırılması amaçlanmıştır. **Gereç ve Yöntemler:** Kliniğimizde bu amaçla psikiyatri bölümünce tarafımıza 2016-2019 yılları arasında opioid bağımlılık tedavisi için cilt altı implant yerleştirilmesi amacıyla yönlendirilen 181 hasta çalışmaya dahil edilmiştir. Demografik özellikler, kaç kez ve hangi bölgelere implantasyon yapıldığı, hastaların tedaviyi yarıda bırakıp bırakmadıkları, eğer bıraktılarsa bırakma nedenleri, enfeksiyon bulgusu varlığı, implant ekstrüzyonu, yapılan ikincil girişimler açısından incelendi. Toplanan veriler analiz edildi. **Bulgular:** Hastaların 95'inde sırt bölgesine, 86'sında ise abdominal bölgeye cilt altı planda naltrekson implant yerleştirilmiştir. Hastalar, ameliyat sonrası dönemde implantların yerleştirildiği bölgeye göre tedavi uyumu, enfeksiyon, ikincil işlem gereksinimi, implant ekstrüzyonu gibi parametreler açısından değerlendirilmiştir. Sırt bölgesine implant yerleştirilen hastaların tedaviye daha iyi uyum sağladığı, daha az ikincil işleme ihtiyaç duydukları, daha az enfeksiyon ve implant ekstrüzyonu ile karşılaşıldığı saptanmıştır. **Sonuç:** Bu bulgular eşliğinde, opioid bağımlılığı tedavisi için cilt altı implantasyon planlanan olgularda, sırt bölgesi abdominal bölgeye kıyasla implantasyon için daha ideal bir alan olma niteliğindedir.

Anahtar Kelimeler: İlaç implantları; naltrekson; opiyat ilişkili bozukluklar; yara enfeksiyonu

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Today, the widespread use of the internet and social media, which are among communication tools, has made it much more convenient and faster to reach anything. Although this situation has advantages, it has also become easier to access substances that are harmful to human health. This has generated a high risk of addiction to substances such as opioids. In a report published by the United Nations in 2019, it was stated that the estimated opioid use worldwide is among 53.3 million people.[1] Opioid use is mostly seen in the young and young adult age groups. The most important problem encountered in these age groups is noncompliance with treatment. Naltrexone, one of the agents used in the treatment of addiction, is a μ-opioid receptor antagonist and blocks the positive effects (euphoria, analgesia) created by opioids.[2-11] While this blockage can be achieved using all forms of naltrexone, which are oral, injectable, or implantable forms, the implantable form minimizes noncompliance to treatment compared to other forms and is used as the first-line treatment of opioid addiction in some centers.[12-17] In the treatment of alcohol addiction in our clinic, the back area is a frequently preferred area for implantation in patients as the difficulty in reaching this part prevents patients from removing the implant on their own.[18] In the studies in the literature, although it is reported that the abdominal region is the preferred implantation site in cases of opioid addiction due to its easy accessibility, there is no study on an ideal implantation site.[19-24] In our study, we aimed to evaluate and compare whether the back or abdominal region is most ideal for implantation by evaluating treatment compliance, surgical wound site, and complications in these patient groups.

MATERIAL AND METHODS

The study was performed in accordance with the Declaration of Helsinki. This study was approved by Gazi University Clinical Research Ethics Committee (date: January 24, 2022, no: ET-22-54). The records of patients who were referred by the psychiatry department for naltrexone implantation for opioid addiction treatment and underwent implantation in our clinic between 2016 and 2019 were retrospectively reviewed both by phone and via computer records. By reviewing the patient files, demographic characteristics, information on the number and site of implantations, whether the patients completed the course of treatment, and the reasons for quitting the treatment, whether there was substance use during the treatment process, the presence and duration of infection after implantation, whether there was an implant extrusion, and whether a secondary procedure was performed for the patients was noted. The missing information was obtained by means of phone calls with the patients.

A total of 181 patients who underwent implantation in the back region during 2016-2017 and in the abdominal region during 2018-2019 and whose records of the above-mentioned questions could be accessed completely were included in the study. The abdominal region was preferred for implantation in the following years (2018-2019) since the patients who were implanted in the back region (between 2016-2017) generally reported discomfort while lying on their back in the early postop period and hypertrophic scarring was observed in some of them. The fact that the abdominal region is the most preferred region in the literature has also been another factor affecting the change of the implantation site.[19-24]

The data obtained were evaluated statistically to compare the implants placed in the back and the abdominal region.

SURGICAL PROCEDURE

In all patients, Naltrexone-containing implant (Prodetoxon® NPK ECHO, Moscow, Russia: 1,000 mg naltrexone, 20 mg triamcinolone acetonide, magnesium stearate) was placed in the back or abdominal area under local anesthesia, by opening a pouch suitable for the implant in the subcutaneous plane under appropriate antiseptic conditions. For implants placed in the back region, an oblique skin incision made at a distance of 1.5-2 cm from the midline in the parascapular region was preferred, whereas lateral incisions made at least 3 cm away from the umbilical region (to protect the paraumbilical perforators) were preferred for implants placed in the abdominal area. Following implantation, the subcutaneous and outer skin layers were repaired. Sutures were removed on the 14th day in all patients (Figure 1).

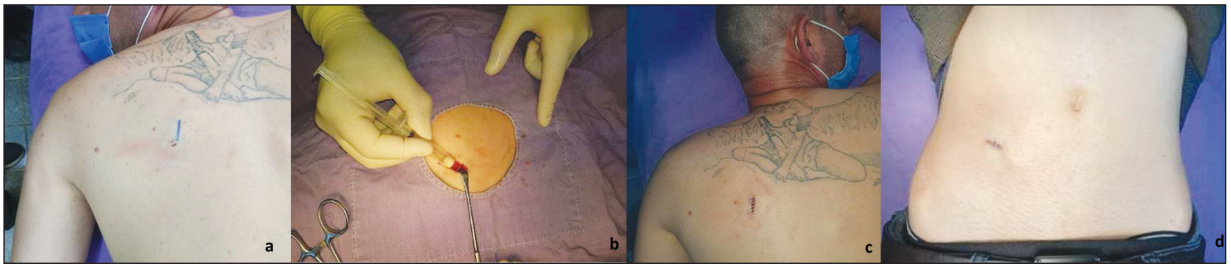

FIGURE 1: Using the parascapular region for implantation in the back area **(a).** Placing the implant in the subcutaneous pouch **(b)**. Suturing **(c)**. Placement of the implant in the lateral umbilicus in the abdominal region **(d)**.

STATISTICAL ANALYSIS

Statistical evaluation was carried out with IBM SPSS 15.0 (SPSS Inc., Chicago, IL, USA) package program. Conformity to normal distribution was evaluated using Kolmogorov-Smirnov test. Numerical variables with normal distribution were represented as mean±standard deviation, and those without normal distribution were represented as median (minimum-maximum). Categorical variables were represented as frequency (percentages). The cut-off values were determined by a receiver operating characteristic (ROC) curve analysis. The relationships between categorical variables were determined using Pearson's chi-square and Fisher's exact tests. A value of $p<0.05$ was considered statistically significant.

RESULTS

The mean age of 181 patients included in the study was 27±6.3, and all of them were male. While the implantation was performed in the back area in 95 (52.5%) cases, it was performed in the abdominal region in 86 (47.5%) cases. In majority of the patients, 3 or fewer implantations were performed (85.6%), and 30% of the patients had discontinued the treatment in terms of treatment compliance. The biggest reason for those who quit the treatment (32.7%) was substance use. In 48 (26.5%) patients, post-implantation infection was encountered, and in most of them (29 cases), the infection regressed with local wound care and appropriate antibiotic therapy. It was observed that the infection lasted more than 4 days in approximately 63% of the infected patients. Implant extrusion was observed in only 19 (10.5%) of 181 patients, and all of them required a secondary revision

TABLE 1: Frequency and percentage values of categorical variables.

n=181	Frequency (%)
Number of implantation	
1.00	57 (31.5)
2.00	63 (34.8)
3.00	35 (19.3)
4.00	12 (6.6)
5.00	7 (3.9)
6.00	4 (2.2)
8.00	1 (0.6)
9.00	1 (0.6)
10.00	1 (0.6)
Receiving treatment	
Received treatment	126 (69.9)
Treatment was interrupted	55 (30.4)
Reasons for interrupting treatment	
Own decision	5 (9.1)
Friend environment	14 (25.5)
Substance use	18 (32.7)
Wound problem	10 (18.2)
Family or financial	4 (7.3)
Does not want to indicate	3 (5.5)
Nausea, decreased appetite	1 (1.8)
Substance use in the treatment process	
No	112 (61.9)
Yes	69 (38.1)
Signs of infection	
Absent	133 (73.5)
Present	48 (26.5)
Duration of infection (days)	
>4 days	31 (63.3)
<4 days	18 (36.7)
Extrusion	
Absent	162 (89.5)
Present	19 (10.5)
Secondary procedures	
No secondary procedures	133 (73.5)
Antibiotic and wound dressing	29 (16.0)
Revision surgery	19 (10.5)
Site of implantation	
Back	95 (52.5)
Abdomen	86 (47.5)

surgery (Table 1). Before performing statistical evaluations, the cut-off value of the relationship between the number of implants and discontinuation of treatment was determined by an ROC curve analysis. Accordingly, the cut-off value of the number of implants that should be inserted in order to quit the treatment was found to be at least 3. Accordingly, whereas only 20.8% of the patients with less than 3 implantations quit the treatment, 49.2% of the patients with more than 3 implantations quit the treatment. This difference was found statistically significant (p<0.001). In the analysis of the relationship between quitting the treatment and continuing opioid use, 94.5% of those who quit the treatment used opioids compared with 13.5% for those who completed the treatment. A statistically significant relationship was found between discontinuation of the treatment and use of opioids during the treatment process (p<0.001). When the effect of post-implant infection on the treatment process was evaluated, 47.9% of the patients with infection discontinued the treatment, while this rate was 24.1% in those without infection. In this respect, a statistically significant relationship was found between the presence of infection and discontinuation of the treatment (p<0.001). While 73.7% of the patients with extrusion discontinued the treatment, this rate was 25.3% in cases without extrusion. A statistically significant difference was found in terms of post-implant extrusion and discontinuation of the treatment (p<0.001).

The cut-off value of the relationship between implant extrusion and the number of implant inserted was determined by an ROC curve analysis. Accordingly, it was observed that the extrusion risk increased significantly in those with 4 or more implant insertion procedures (78.9%) compared to those with less than 4 (6.8%) (p<0.001) (Table 2).

TABLE 2: Statistical analysis of the relationship between number of implantation and extrusion status.

	Number of implantation		p value
Extrusion	Below 4	4 and above	<0.001**
Absent	151 (93.2%)	11 (6.8%)	
Present	4 (21.1%)	15 (78.9%)	

**Fisher exact test.

In the statistical evaluation made in terms of the relationship between the implantation site and discontinuation of treatment, 12.6% of the patients with implants in the back region discontinued the treatment, while this rate was found to be 50% in the patients with implants in the abdominal region. Accordingly, the implant location was found to be a factor that had a significant effect on discontinuing the treatment (p<0.001) (Table 3).

In the evaluation made in terms of the relationship between the implantation site and signs of infection, infection was detected in 11.6% of the patients with implants in the back region, while 43% of the patients with implants in the abdominal area were infected. This difference was statistically significant (p<0.001) (Table 4).

In the analysis of the relationship between the site of implantation and implant extrusion, extrusion was encountered in 3.2% of the implants placed in

TABLE 3: Statistical analysis in terms of site of implantation and discontinuation of treatment

	Discontinuation of treatment		p value
Site of implantation	No	Yes	<0.001*
Back	83 (87.4%)	12 (12.6%)	
Abdomen	43 (50.0%)	43 (50.0%)	

*Pearson chi-square test.

TABLE 4: Statistical analysis of the relationship between the site of implantation and signs of infection.

	Signs of infection		p value
Site of implantation	Absent	Present	<0.001*
Back	84 (88.4%)	11 (11.6%)	
Abdomen	49 (57.0%)	37 (43.0%)	

*Pearson chi-square test.

TABLE 5: Statistical analysis of the assessment in terms of site of implantation and implant extrusion.

	Extrusion		p value
Site of implantation	Absent	Present	0.001*
Back	92 (96.8%)	3 (3.2%)	
Abdomen	70 (81.4%)	16 (18.6%)	

*Pearson chi-square test.

TABLE 6: Statistical analysis in terms of site of implantation and secondary procedures.

	Secondary procedures			p value
Site of implantation	No secondary procedure	Antibiotic and wound dressing	Revision surgery	<0.001*
Back	85 (89.5%)	7 (7.4%)	3 (3.2%)	
Abdomen	48 (55.8%)	22 (25.6%)	16 (18.6%)	

*Pearson chi-square test.

the back region and in 18.6% of the implants placed in the abdominal region. A statistically significant difference was found in the evaluation of this relationship between implantation location and extrusion rates (p<0.001) (Table 5).

In the evaluation made in terms of implantation site and conditions requiring secondary procedures related to the implant, it was determined that 10.6% of the implants placed in the back required secondary procedures (7.4% wound care, 3.2% revision surgery), whereas this rate was 44.2% (25.6% wound care, 18.6% revision surgery) for implants placed in the abdominal area. Accordingly, a significant relationship was found between the location of implants and secondary procedures (p<0.001) (Table 6).

The cut-off value of the relationship between infection time and implant extrusion was determined by ROC curve analysis. Accordingly, it was found that the risk of implant extrusion increased significantly in patients with an infection period of more than 4 days (p<0.001).

In the statistical analysis performed in terms of requirement of a secondary procedure (infection scenario requiring antibiotic treatment and revision surgery) in patients undergoing implant treatment and discontinuing the treatment, 24.1% of the patients who did not undergo a secondary procedure quit the treatment, while this rate was 47.9% in patients who had a secondary procedure. This difference was statistically significant (p<0.001).

DISCUSSION

Today, opioid receptor antagonists are a widely used treatment method in opioid addiction. In the literature, it has been stated that the use of implantable naltrexone in opioid antagonism is a promising alternative to other conventional treatment methods.[2,13,25,26] The long duration of action of naltrexone implants is an important advantage. However, the major disadvantages of these implants are that they require surgical procedures for placement and may cause a local tissue reaction (Figure 2). There are a limited number of studies evaluating the side effects of implants with regard to the area where implants are placed, and cases with problems such as erythema, swelling, wound infection, wound dehiscence, itching, pain, and necrosis have been reported.[16,27] Implant-related complications and local tissue reactions were found to be present at varying rates of 2-32.8%.[12,15,22,25-34] Although Prodetoxon® (NPK ECHO, Moscow, Russia) implants applied in

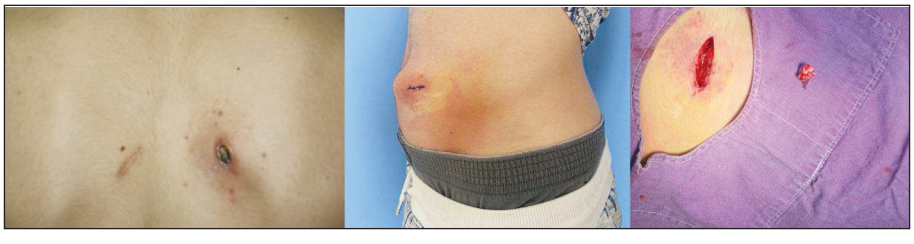

FIGURE 2: Discharge and wound site requiring debridement in the right parascapular region 6 weeks after implantation **(a)**. The patient who presented with swelling, redness, and itching after implantation in the abdominal region **(b)**. Removal of the implants and incomplete resorption **(c)**.

our clinic contain triamcinolone, a long-acting steroid to reduce local tissue reactions, 48 (26.5%) of 181 patients in our series had complications, and this rate was found to be similar to those in the literature. The fact that there is a significant relationship between the number of implant insertions and discontinuation of treatment indicates that repetitive applications (e.g., three or more) decrease patient compliance and are less tolerated. The increased side effects (local tissue reaction) experienced by the patient as the number of implant insertion procedure increased was interpreted as the reason for the occurrence of this result. Choosing the cases that are expected to be treated with 3 or fewer applications by the psychiatry department in treatment planning may be effective in increasing the success of the treatment. The significant relationship between quitting the treatment and substance use during treatment was interpreted as follows: discontinuing treatment is one of the primary major factors on opioid use. The use of other addiction treatment modalities combined with implant therapy in patients with poor treatment compliance and severe opioid addiction may be an alternative to the solution of this problem. The significant relationship found between wound site infection and discontinuation of treatment indicates that infection is an effective factor in discontinuing addiction treatment. Therefore, it is important to pay attention to surgical antisepsis rules, use appropriate prophylactic antibiotics, and show maximum sensitivity to wound care in patients scheduled for implantation. Implant extrusion is one of the factors that could lead to discontinuing the treatment, just like wound site infection. In extrusion cases, with aggressive wound care and appropriate treatment, the healing process should be accelerated, and the risk of implant removal should be minimized. In this process, continuity of treatment and close patient follow-up should be ensured. It was thought that significant increase in the number of implant insertions and the risk of extrusion might be due to scar tissue, decreased vascularity and the inflammatory response of the implant as a result of incomplete absorption from the scarred bed caused by repeated surgical interventions in the same area (Table 2). In repeated multiple implantations (e.g., 4 and more applications), the selection of different anatomical regions may reduce the risk of extrusion. The fact that patients with implants in the back region were more likely to adapt to the treatment compared to those with abdominal implants, required secondary procedures less often (infection requiring local wound care, extrusion requiring revision surgery), had less infection and encountered implant extrusion less often suggests that the back area might be a more reliable area in terms of implantation and cannot be reached by the patient (Table 2, Table 3, Table 4, Table 5, Table 6). Although it has not been defined in the literature, it has been mentioned that when patients develop withdrawal symptoms, they may attempt to remove the implant. In such a situation, the easy accessibility of the lower abdominal area increases the risk in this sense.[16] In addition, in some patients, implantation in the lower abdominal region may cause discomfort because it coincides with the belt-wearing area. Further, in the patient group with mostly low body mass index, very thin abdominal skin layers may pose a risk in terms of extrusion.

The correlation between prolonged infection time (>4 days) and extrusion risk was attributed to the increase in surrounding tissue damage caused by prolonged inflammation. Therefore, in cases with suspected infection, it will be appropriate to eliminate the infection as soon as possible and to follow it closely by providing aggressive wound care and early broad-spectrum antibiotic treatment.

It was observed that the probability of discontinuing the treatment increased as secondary procedures were performed in patients, and this rate was found to be the highest in patients who underwent revision surgery. It has been interpreted that additional morbidity caused by additional surgical interventions in patients causes discontinuation of the treatment.

Although it has been reported that the abdominal region is mostly preferred as the implantation site in patients with opioid-dependence who have undergone subcutaneous implantation, there is no comparative study on implantations performed in different anatomical regions on this subject. Our study is the first study in the literature in this aspect.

Although hospital records are taken as reference in the study, receiving additional information from patients and their relatives by phone may have led to subjective data being collected. In addition, the retrospective nature of our study contributes to its limitation. A prospective study using objective criteria such as urine opioid analysis in the evaluation of opioid addiction will be more guiding in this area.

CONCLUSION

In the light of the results obtained in our study, the back area is a more suitable area for implantation compared to the abdominal region in these patient groups due to reasons such as providing better treatment continuity, requiring less secondary procedures, encountering less infection and extrusions, and being in an area that the patient cannot easily reach in case of withdrawal symptoms. Hence, following these evaluations, we recommend that the back area should be preferred as the primary area for implantation.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Serhat Şibar;* ***Design:*** *Erkan Deniz;* ***Control/Supervision:*** *Serhat Şibar;* ***Data Collection and/or Processing:*** *Oğuzhan Karasu;* ***Analysis and/or Interpretation:*** *Oğuzhan Karasu, Buğra Demirbaş;* ***Literature Review:*** *Erkan Deniz, Buğra Demirbaş;* ***Writing the Article:*** *Serhat Şibar;* ***Critical Review:*** *Melike Küükkarapınar;* ***References and Fundings:*** *Serhat Şibar;* ***Materials:*** *Serhat Şibar.*

REFERENCES

1. UNODC. Drug Use. [Cited: Sep 28, 2022]. Available from: [Link]
2. Larney S, Gowing L, Mattick RP, Farrell M, Hall W, Degenhardt L. A systematic review and meta-analysis of naltrexone implants for the treatment of opioid dependence. Drug Alcohol Rev. 2014;33(2):115-28. [Crossref] [PubMed]
3. Veilleux JC, Colvin PJ, Anderson J, York C, Heinz AJ. A review of opioid dependence treatment: pharmacological and psychosocial interventions to treat opioid addiction. Clin Psychol Rev. 2010;30(2):155-66. [Crossref] [PubMed]
4. Van den Brink W, Haasen C. Evidenced-based treatment of opioid-dependent patients. Can J Psychiatry. 2006;51(10):635-46. [Crossref] [PubMed]
5. Oviedo-Joekes E, Brissette S, Marsh DC, Lauzon P, Guh D, Anis A, et al. Diacetylmorphine versus methadone for the treatment of opioid addiction. N Engl J Med. 2009;361(8):777-86. [Crossref] [PubMed] [PMC]
6. Johnson RE, Chutuape MA, Strain EC, Walsh SL, Stitzer ML, Bigelow GE. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. N Engl J Med. 2000;343(18):1290-7. [Crossref] [PubMed]
7. Garbutt JC, Kranzler HR, O'Malley SS, Gastfriend DR, Pettinati HM, Silverman BL, et al; Vivitrex Study Group. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. JAMA. 2005;293(13):1617-25. [Crossref] [PubMed]
8. Gonzalez JP, Brogden RN. Naltrexone. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the management of opioid dependence. Drugs. 1988;35(3):192-213. [Crossref] [PubMed]
9. Erdoğan A, Topcuoğlu M, Coşkun MN, Cinemre B, Kulaksızoğlu B, Kuloğlu MM. Comparison of naltrexone implant and oral buprenorphine-naloxone in the treatment of opiate use disorder. Hum Psychopharmacol. 2022;37(2):e2813. [Crossref] [PubMed]
10. Kuppalli S, Seth R, Orhurhu V, Urits I, Kaye AD, Hunter C, et al. Recent advances in the treatment of opioid use disorder. Curr Pain Headache Rep. 2021;25(4):23. [Crossref] [PubMed]
11. Kelty E, Joyce D, Hulse G. A retrospective cohort study of mortality rates in patients with an opioid use disorder treated with implant naltrexone, oral methadone or sublingual buprenorphine. Am J Drug Alcohol Abuse. 2019;45(3):285-91. [Crossref] [PubMed]
12. Tiihonen J, Krupitsky E, Verbitskaya E, Blokhina E, Mamontova O, Föhr J, et al. Naltrexone implant for the treatment of polydrug dependence: a randomized controlled trial. Am J Psychiatry. 2012;169(5):531-6. [Crossref] [PubMed]
13. 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(2):264-71. [Crossref] [PubMed] [PMC]
14. Colquhoun RM. Open label trial of naltrexone implants: measuring blood serum levels of naltrexone. Subst Abuse. 2013;7:75-84. [Crossref] [PubMed] [PMC]
15. Hulse GK, Morris N, Arnold-Reed D, Tait RJ. Improving clinical outcomes in treating heroin dependence: randomized, controlled trial of oral or implant naltrexone. Arch Gen Psychiatry. 2009;66(10):1108-15. [Crossref] [PubMed]

16. Kunøe N, Lobmaier P, Vederhus JK, Hjerkinn B, Hegstad S, Gossop M, et al. Naltrexone implants after in-patient treatment for opioid dependence: randomised controlled trial. Br J Psychiatry. 2009;194(6):541-6. [Crossref] [PubMed]
17. Krupitsky E, Zvartau E, Woody G. Use of naltrexone to treat opioid addiction in a country in which methadone and buprenorphine are not available. Curr Psychiatry Rep. 2010;12(5):448-53. [Crossref] [PubMed] [PMC]
18. Sezgin B, Sibar S, Bulam H, Findikcioglu K, Tuncer S, Dogan B. Disulfiram implantation for the treatment of alcoholism: clinical experiences from the plastic surgeon's point of view. Arch Plast Surg. 2014;41(5):571-5. [Crossref] [PubMed] [PMC]
19. Lobmaier PP, Kunøe N, Gossop M, Waal H. Naltrexone depot formulations for opioid and alcohol dependence: a systematic review. CNS Neurosci Ther. 2011;17(6):629-36. [Crossref] [PubMed] [PMC]
20. Comer SD, Sullivan MA, Hulse GK. Sustained-release naltrexone: novel treatment for opioid dependence. Expert Opin Investig Drugs. 2007;16(8):1285-94. [Crossref] [PubMed]
21. Foster J, Brewer C, Steele T. Naltrexone implants can completely prevent early (1-month) relapse after opiate detoxification: a pilot study of two cohorts totalling 101 patients with a note on naltrexone blood levels. Addict Biol. 2003;8(2):211-7. [Crossref] [PubMed]
22. Carre-o JE, Alvarez CE, Narciso GI, Bascarán MT, Díaz M, Bobes J. Maintenance treatment with depot opioid antagonists in subcutaneous implants: an alternative in the treatment of opioid dependence. Addict Biol. 2003;8(4):429-38. [Crossref] [PubMed]
23. Hulse GK, Arnold-Reed DE, O'Neil G, Chan CT, Hansson R, O'Neil P. Blood naltrexone and 6-beta-naltrexol levels following naltrexone implant: comparing two naltrexone implants. Addict Biol. 2004;9(1):59-65. [Crossref] [PubMed]
24. Edinoff AN, Nix CA, Orellana CV, StPierre SM, Crane EA, Bulloch BT, et al. Naltrexone implant for opioid use disorder. Neurol Int. 2021;14(1):49-61. [Crossref] [PubMed] [PMC]
25. Jhugroo A, Ellayah D, Norman A, Hulse G. Naltrexone implant treatment for buprenorphine dependence--Mauritian case series. J Psychopharmacol. 2014;28(8):800-3. [Crossref] [PubMed]
26. Waal H, Frogopsahl G, Olsen L, Christophersen AS, Mørland J. Naltrexone implants -- duration, tolerability and clinical usefulness. A pilot study. Eur Addict Res. 2006;12(3):138-44. [Crossref] [PubMed]
27. Krupitsky E, Zvartau E, Blokhina E, Verbitskaya E, Wahlgren V, Tsoy-Podosenin M, et al. Randomized trial of long-acting sustained-release naltrexone implant vs oral naltrexone or placebo for preventing relapse to opioid dependence. Arch Gen Psychiatry. 2012;69(9):973-81. [Crossref] [PubMed] [PMC]
28. Lobmaier PP, Kunøe N, Gossop M, Katevoll T, Waal H. Naltrexone implants compared to methadone: outcomes six months after prison release. Eur Addict Res. 2010;16(3):139-45. [Crossref] [PubMed]
29. Reece AS. Comparative treatment and mortality correlates and adverse event profile of implant naltrexone and sublingual buprenorphine. J Subst Abuse Treat. 2009;37(3):256-65. [Crossref] [PubMed]
30. Lintzeris N, Lee S, Scopelliti L, Mabbutt J, Haber PS. Unplanned admissions to two Sydney public hospitals after naltrexone implants. Med J Aust. 2008;188(8):441-4. [Crossref] [PubMed]
31. Ak S, Can Gürel Ş. Letter to the editor - drug eruption after sustained release naltrexone pellet implantation. Turk Psikiyatri Derg. 2020;31(2):146-7. [PubMed]
32. Bal C, Rappersberger K, Posch C. Adverse effects of subcutaneous, drug-releasing implants for the treatment of opioid drug addiction. J Dtsch Dermatol Ges. 2017;15(12):1232-4. [Crossref] [PubMed]
33. Singh PA, Cassel KP, Moscati RM, Eckersley D. Acute generalized erythrodermic pustular psoriasis associated with bupropion/naltrexone (Contrave®). J Emerg Med. 2017;52(4):e111-3. [Crossref] [PubMed]
34. Heck J, Burda K, Hillemacher T, Bleich S, Stichtenoth DO, Groh A. Naltrexone-induced drug eruption. Clin Case Rep. 2020;8(10):2049-50. [Crossref] [PubMed] [PMC]