

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX INC.
Petitioners

v.

ALKERMES PHARMA IRELAND LIMITED
Patent Owner

Case No. IPR2025-00514
Patent 7,919,499

DECLARATION OF JUNE ANN MUNFORD

1. My name is June Ann Munford. I am over the age of 18, have personal knowledge of the facts set forth herein, and am competent to testify to the same.

2. I earned a Master of Library and Information Science (MLIS) from the University of Wisconsin-Milwaukee in 2009. I have over ten years of experience in the library/information science field. Beginning in 2004, I have served in various positions in the public library sector including Assistant Librarian, Youth Services Librarian and Library Director. I have attached my Curriculum Vitae as Appendix CV.

3. During my career in the library profession, I have been responsible for materials acquisition for multiple libraries. In that position, I have cataloged, purchased and processed incoming library works. That includes purchasing materials directly from vendors, recording publishing data from the material in question, creating detailed material records for library catalogs and physically preparing that material for circulation. In addition to my experience in acquisitions, I was also responsible for analyzing large collections of library materials, tailoring library records for optimal catalog search performance and creating lending agreements between libraries during my time as a Library Director.

4. I am fully familiar with the catalog record creation process in the library sector. In preparing a material for public availability, a library catalog record

describing that material would be created. These records are typically written in Machine Readable Catalog (herein referred to as “MARC”) code and contain information such as a physical description of the material, metadata from the material’s publisher, and date of library acquisition. In particular, the 008 field of the MARC record is reserved for denoting the date of creation of the library record itself. As this typically occurs during the process of preparing materials for public access, it is my experience that an item’s MARC record indicates the date of an item’s public availability.

5. Typically, in creating a MARC record, a librarian would gather various bits of metadata such as book title, publisher and subject headings among others and assign each value to a relevant numerical field. For example, a book’s physical description is tracked in field 300 while title/attribution is tracked in field 245. The 008 field of the MARC record is reserved for denoting the creation of the library record itself. As this is the only date reflecting the inclusion of said materials within the library’s collection, it is my experience that an item’s 008 field accurately indicates the date of an item’s public availability.

6. I am familiar with the Internet Archive, a digital library accessible to the general public. Among other services that the Internet Archive makes available to the general public is the Wayback Machine, an online archive of the web. The Internet Archive’s Wayback Machine service archives webpages as of a certain

capture date to track changes in the web over time. The Internet Archive has been in operation as a nonprofit library since 1996 and has hosted the Wayback Machine service since its inception in 2001. During my time as a librarian, I frequently used the Internet Archive's Wayback Machine for research and instruction purposes. This includes teaching instructional classes on using the Wayback Machine to library patrons and using the Wayback Machine to research reference inquiries that require hard-to-find online resources. I consider the Internet Archive's records keeping to be as rigorous and detailed as other formal library records keeping practices such as MARC records, OCLC records and Dublin Core.

7. I understand that both parties in this case have presented different definitions of a Person of Ordinary Skill in the Art (POSITA), a common legal term. As I have no background in the law or its practice, my understanding of a POSITA is restricted to the POSITA's ability to access a publicly available piece of artwork. For the purposes of this declaration, my determinations are based on a POSITA being a person who has a professional relationship to a given subject or a formal education on a given subject from a reputable educational institution. As my determinations are based on library catalog records, it should be noted that any POSITA pursuing materials discussed in this declaration would have access to library professionals with a background or education in library sciences such as research, indexing and collection management.

8. I have reviewed Exhibit 1004, "Depot Naltrexone: Long-Lasting Antagonism of the Effects of Heroin in Humans" by Sandra D. Comer, et al as published in Psychopharmacology February 2002.

9. Attached hereto as Appendix COMER01 is a true and correct copy of the MARC record for Psychopharmacology as held by the Penn State University Library. I secured this record myself from the library's public catalog. The MARC record contained within Appendix COMER01 accurately describes the title, publisher and ISSN number of Psychopharmacology. The Showing Results field present on page 4 of this record indicates the library's collection includes the February 2002 issue of Psychopharmacology containing "Depot Naltrexone: Long-Lasting Antagonism of the Effects of Heroin in Humans".

10. Attached hereto as Appendix COMER02 is a true and correct copy of "Depot Naltrexone: Long-Lasting Antagonism of the Effects of Heroin in Humans" as published in Psychopharmacology as held by the Penn State University Library. These scans were secured from the library's collection. In comparing Exhibit 1004 to Appendix COMER02, it is my determination that Exhibit 1004 is a true and correct copy of "Depot Naltrexone: Long-Lasting Antagonism of the Effects of Heroin in Humans" by Sandra D. Comer, et al as published in Psychopharmacology.

11. The 008 field of the MARC record in Appendix COMER01 indicates the date of record creation. The 008 field of Appendix COMER01 indicates the Penn

State University Library first acquired Psychopharmacology as of March 20, 1998 and held the journal in perpetuity until the publication of "Depot Naltrexone: Long-Lasting Antagonism of the Effects of Heroin in Humans". Considering this information, it is my determination that Psychopharmacology February 2002 and therefore "Depot Naltrexone: Long-Lasting Antagonism of the Effects of Heroin in Humans" was made available to the public shortly after its initial publication in February 2002 and certainly no later than December 31, 2002.

12. Attached hereto as Appendix COMER03 is a true and correct copy of the MARC record for Psychopharmacology as held by the Penn State University Library. I secured this record myself from the library's public catalog. The MARC record contained within Appendix COMER03 accurately describes the title, publisher and ISSN number of Psychopharmacology . The Availability field present on page 3 of this record indicates the library's collection includes the February 2002 issue of Psychopharmacology containing "Depot Naltrexone: Long-Lasting Antagonism of the Effects of Heroin in Humans".

13. Attached hereto as Appendix COMER04 is a true and correct copy of "Depot Naltrexone: Long-Lasting Antagonism of the Effects of Heroin in Humans" as published in Psychopharmacology as held by the Penn State University Library. These scans were secured from the library's collection. In comparing Exhibit 1004 to Appendix COMER04, it is my determination that Exhibit 1004 is a true and

correct copy of "Depot Naltrexone: Long-Lasting Antagonism of the Effects of Heroin in Humans" by Sandra D. Comer, et al as published in Psychopharmacology.

14. The 008 field of the MARC record in Appendix COMER03 indicates the date of record creation. The 008 field of Appendix COMER03 indicates the Penn State University Library first acquired Psychopharmacology as of January 23, 1984 and held the journal in perpetuity until the publication of "Depot Naltrexone: Long-Lasting Antagonism of the Effects of Heroin in Humans" . Considering this information, it is my determination that Psychopharmacology February 2002 and therefore "Depot Naltrexone: Long-Lasting Antagonism of the Effects of Heroin in Humans" was made available to the public shortly after its initial publication in February 2002.

15. I have reviewed Exhibit 1006, "Naltrexone Versus Acamprosate: One Year Follow-Up of Alcohol Dependence Treatment" by G. Rubio, et al as published in Alcohol and Alcoholism October 2001.

16. Attached hereto as Appendix RUBIO01 is a true and correct copy of the MARC record for Alcohol and Alcoholism as held by the Penn State University Library. I secured this record myself from the library's public catalog. The MARC record contained within Appendix RUBIO01 accurately describes the title, publisher and ISSN number of Alcohol and Alcoholism. The Showing Results field present on page 4 of this record indicates the library's collection includes the October 2001 issue

of Alcohol and Alcoholism containing "Naltrexone Versus Acamprosate: One Year Follow-Up of Alcohol Dependence Treatment".

17. Attached hereto as Appendix RUBIO02 is a true and correct copy of "Naltrexone Versus Acamprosate: One Year Follow-Up of Alcohol Dependence Treatment" as published in Alcohol and Alcoholism as held by the Penn State University Library. This PDF was secured from the library's collection. In comparing Exhibit 1006 to Appendix RUBIO02, it is my determination that Exhibit 1006 is a true and correct copy of "Naltrexone Versus Acamprosate: One Year Follow-Up of Alcohol Dependence Treatment" by G. Rubio, et al as published in Alcohol and Alcoholism.

18. The 008 field of the MARC record in Appendix RUBIO01 indicates the date of record creation. The 008 field of Appendix RUBIO01 indicates the Penn State University Library first acquired Alcohol and Alcoholism as of July 27, 1999 and held the journal in perpetuity until the publication of "Naltrexone Versus Acamprosate: One Year Follow-Up of Alcohol Dependence Treatment". Considering this information, it is my determination that Alcohol and Alcoholism October 2001 and therefore "Naltrexone Versus Acamprosate: One Year Follow-Up of Alcohol Dependence Treatment" was made available to the public shortly after its initial publication in October 2001 and certainly no later than December 31, 2001.

19. Attached hereto as Appendix RUBIO03 is a true and correct copy of the MARC record for Alcohol and Alcoholism as held by the Penn State University Library. I secured this record myself from the library's public catalog. The MARC record contained within Appendix RUBIO03 accurately describes the title, publisher and ISSN number of Alcohol and Alcoholism. The Availability field present on page 3 of this record indicates the library's collection includes the October 2001 issue of Alcohol and Alcoholism containing "Naltrexone Versus Acamprosate: One Year Follow-Up of Alcohol Dependence Treatment".

20. Attached hereto as Appendix RUBIO04 is a true and correct copy of "Naltrexone Versus Acamprosate: One Year Follow-Up of Alcohol Dependence Treatment" as published in Alcohol and Alcoholism as held by the Penn State University Library. These scans were secured from the library's collection. In comparing Exhibit 1006 to Appendix RUBIO04, it is my determination that Exhibit 1006 is a true and correct copy of "Naltrexone Versus Acamprosate: One Year Follow-Up of Alcohol Dependence Treatment" by G. Rubio, et al as published in Alcohol and Alcoholism.

21. The 008 field of the MARC record in Appendix RUBIO03 indicates the date of record creation. The 008 field of Appendix RUBIO03 indicates the Penn State University Library first acquired Alcohol and Alcoholism as of January 23, 1984 and held the journal in perpetuity until the publication of "Naltrexone Versus

Acamprosate: One Year Follow-Up of Alcohol Dependence Treatment". Considering this information, it is my determination that Alcohol and Alcoholism October 2001 and therefore "Naltrexone Versus Acamprosate: One Year Follow-Up of Alcohol Dependence Treatment" was made available to the public shortly after its initial publication in October 2001.

22. I have reviewed Exhibit 1008, "Sustained-Release Naltrexone for Alcoholism Treatment: A Preliminary Study" by Henry R. Kranzler as published in Alcohol: Clinical and Experimental Research August 1998.

23. Attached hereto as Appendix KRANZLER01 is a true and correct copy of the MARC record for Alcohol: Clinical and Experimental Research as held by the Penn State University Library. I secured this record myself from the library's public catalog. The MARC record contained within Appendix KRANZLER01 accurately describes the title, publisher and ISSN number of Alcohol: Clinical and Experimental Research. The Showing Results field present on page 5 of this record indicates the library's collection includes the August 1998 issue of Alcohol: Clinical and Experimental Research containing "Sustained-Release Naltrexone for Alcoholism Treatment: A Preliminary Study".

24. Attached hereto as Appendix KRANZLER02 is a true and correct copy of "Sustained-Release Naltrexone for Alcoholism Treatment: A Preliminary Study" as published in Alcohol: Clinical and Experimental Research as held by the Penn

State University Library. This PDF was secured from the library's collection. In comparing Exhibit 1008 to Appendix KRANZLER02, it is my determination that Exhibit 1008 is a true and correct copy of "Sustained-Release Naltrexone for Alcoholism Treatment: A Preliminary Study" by Henry R. Kranzler as published in Alcohol: Clinical and Experimental Research.

25. The 008 field of the MARC record in Appendix KRANZLER01 indicates the date of record creation. The 008 field of Appendix KRANZLER01 indicates the Penn State University Library first acquired Alcohol: Clinical and Experimental Research as of May 8, 2000, with a publication history including "Sustained-Release Naltrexone for Alcoholism Treatment: A Preliminary Study". Considering this information, it is my determination that Alcohol: Clinical and Experimental Research August 1998 and therefore "Sustained-Release Naltrexone for Alcoholism Treatment: A Preliminary Study" was made available to the public via Penn State University Library shortly after its initial acquisition soon after May 8, 2000 and likely earlier via the issue's original publication in August 1998.

26. I have reviewed Exhibit 1010, "Clinical Evaluation of A Naltrexone Sustained-Release Preparation" by C.N. Chiang, et al as published in Drug & Alcohol Dependence September 1985.

27. Attached hereto as Appendix CHIANG01 is a true and correct copy of the MARC record for Drug & Alcohol Dependence as held by the University of

Wisconsin Library. I secured this record myself from the library's public catalog. The MARC record contained within Appendix CHIANG01 accurately describes the title, publisher and ISSN number of *Drug & Alcohol Dependence*. The Physical Locations field present on page 5 of this record indicates the library's collection includes the September 1985 issue of *Drug & Alcohol Dependence* containing "Clinical Evaluation of A Naltrexone Sustained-Release Preparation".

28. Attached hereto as Appendix CHIANG02 is a true and correct copy of "Clinical Evaluation of A Naltrexone Sustained-Release Preparation" as published in *Drug & Alcohol Dependence* as held by the University of Wisconsin Library. These scans were secured from the library's collection. In comparing Exhibit 1010 to Appendix CHIANG02, it is my determination that Exhibit 1010 is a true and correct copy of "Clinical Evaluation of A Naltrexone Sustained-Release Preparation" by C.N. Chiang, et al as published in *Drug & Alcohol Dependence*.

29. The 008 field of the MARC record in Appendix CHIANG01 indicates the date of record creation. The 008 field of Appendix CHIANG01 indicates the University of Wisconsin Library first acquired *Drug & Alcohol Dependence* as of November 21, 1975 and held the journal in perpetuity until the publication of "Clinical Evaluation of A Naltrexone Sustained-Release Preparation". Considering this information, it is my determination that *Drug & Alcohol Dependence* September 1985 and therefore "Clinical Evaluation of A Naltrexone Sustained-Release

Preparation" was made available to the public shortly after its initial publication in September 1985.

30. I have reviewed Exhibit 1011, "Tolerability Study of A Depot Form of Naltrexone Substance Abusers" by T.N. Alim, et al as published in Proceedings of the Problems of Drug Dependence 1994.

31. Attached hereto as Appendix ALIM01 is a true and correct copy of the MARC record for Proceedings of the Problems of Drug Dependence as held by the Penn State University Library. I secured this record myself from the library's public catalog. The MARC record contained within Appendix ALIM01 accurately describes the title, conference title and publisher number of Proceedings of the Problems of Drug Dependence. The Availability field present on page 3 of this record indicates the library's collection includes the 1994 edition of Proceedings of the Problems of Drug Dependence containing "Tolerability Study of A Depot Form of Naltrexone Substance Abusers". In comparing Exhibit 1011 to Appendix ALIM01, it is my determination that Exhibit 1011 is a true and correct copy of "Tolerability Study of A Depot Form of Naltrexone Substance Abusers" by T.N. Alim, et al as published in Proceedings of the Problems of Drug Dependence 1994.

32. The 008 field of the MARC record in Appendix ALIM01 indicates the date of record creation. The 008 field of Appendix ALIM01 indicates the Penn State University Library first acquired their collection of Proceedings of the Problems of

Drug Dependence as of March 28, 1995. Considering this information, it is my determination that Proceedings of the Problems of Drug Dependence 1994 and therefore "Tolerability Study of A Depot Form of Naltrexone Substance Abusers" was made available to the public via the Penn State University Library shortly after March 28, 1995 and likely earlier via the original conference in 1994.

33. I have reviewed Exhibit 1014, "Safety And Pharmacokinetics of a New Formulation of Depot Naltrexone" by S.J. Heishman, et al as published in Proceedings of the Problems of Drug Dependence 1993.

34. Attached hereto as Appendix HEISHMAN01 is a true and correct copy of the MARC record for Proceedings of the Problems of Drug Dependence as held by the Penn State University Library. I secured this record myself from the library's public catalog. The MARC record contained within Appendix HEISHMAN01 accurately describes the title, conference title and publisher of Proceedings of the Problems of Drug Dependence. The Availability field present on page 3 of this record indicates the library's collection includes the 1993 edition of Proceedings of the Problems of Drug Dependence containing "Safety And Pharmacokinetics of a New Formulation of Depot Naltrexone". In comparing Exhibit 1014 to Appendix HEISHMAN01, it is my determination that Exhibit 1014 is a true and correct copy of "Safety And Pharmacokinetics of a New Formulation of Depot Naltrexone" by

S.J. Heishman, et al as published in Proceedings of the Problems of Drug Dependence 1993.

35. The 008 field of the MARC record in Appendix HEISHMAN01 indicates the date of record creation. The 008 field of Appendix HEISHMAN01 indicates the Penn State University Library first acquired their collection of Proceedings of the Problems of Drug Dependence as of March 28, 1995. Considering this information, it is my determination that Proceedings of the Problems of Drug Dependence 1993 and therefore "Safety And Pharmacokinetics of a New Formulation of Depot Naltrexone" was made available to the public via the Penn State University Library shortly after March 28, 1995 and likely earlier via the original conference in 1993.

36. I have reviewed Exhibit 1016, a document entitled Evidence for the Efficacy of Naltrexone in the Treatment of Alcohol Dependence (Alcoholism).

37. Attached hereto as Appendix LEAVITT01 is a screen capture of the Internet Archive Wayback Machine entry for http://www.atforum.com:80/SiteRoot/pages/addiction_resources/addiction_resources.shtml. I secured these screen captures myself from https://web.archive.org/web/20021004183904/http://www.atforum.com:80/SiteRoot/pages/addiction_resources/addiction_resources.shtml. This record was captured as of October 4, 2002.

38. Appendix LEAVITT01 is an Internet Archive capture of a web page entitled Addiction Resources as hosted on the Addiction Treatment Forum website. This page contains a list of documents published by Addiction Treatment Forum with an entry for “Evidence for the Efficacy of Naltrexone in the Treatment of Alcohol Dependence (Alcoholism)” visible on page 2. This entry for the Leavitt paper contains a link titled ‘Naltrexone White Paper.pdf’. Clicking on this link presents the webpage user with a PDF copy of the Leavitt paper, included in this declaration at Appendix LEAVITT02. As this page was captured by the Internet Archive as of October 4, 2002, it is my determination that “Evidence for the Efficacy of Naltrexone in the Treatment of Alcohol Dependence (Alcoholism)” was first made available to the public via the Addiction Treatment Forum website as of October 4, 2002.

39. Attached hereto as Appendix LEAVITT02 is a screen capture of the Internet Archive Wayback Machine entry for http://www.atforum.com/SiteRoot/pages/addiction_resources/NaltrexoneWhitePaper.pdf. I secured these screen captures myself from https://web.archive.org/web/20050701000000*/http://www.atforum.com/SiteRoot/pages/addiction_resources/NaltrexoneWhitePaper.pdf.

40. Appendix LEAVITT02 is an Internet Archive capture of a PDF copy of “Evidence for the Efficacy of Naltrexone in the Treatment of Alcohol Dependence

(Alcoholism)” as hosted on the Addiction Treatment Forum website. In comparing Appendix LEAVITT02 to Exhibit 1016, it is my determination that Exhibit 1016 is a true and correct copy of “Evidence for the Efficacy of Naltrexone in the Treatment of Alcohol Dependence (Alcoholism)”.

41. I have reviewed Exhibit 1019, "Kinetics of a naltrexone sustained-release preparation" by C.N. Chiang, et al. as published in Clinical Pharmacology and Therapeutics November 1984.

42. Attached hereto as Appendix CHIANG03 is a true and correct copy of the MARC record for Clinical Pharmacology and Therapeutics as held by the Penn State University Library. I secured this record myself from the library’s public catalog. The MARC record contained within Appendix CHIANG03 accurately describes the title, publisher and ISSN number of Clinical Pharmacology and Therapeutics. The Showing Results field present on page 5 of this record indicates the library's collection includes the November 1984 issue of Clinical Pharmacology and Therapeutics containing "Kinetics of a naltrexone sustained-release preparation".

43. Attached hereto as Appendix CHIANG04 is a true and correct copy of "Kinetics of a naltrexone sustained-release preparation" as published in Clinical Pharmacology and Therapeutics as held by the Penn State University Library. This PDF was secured from the library’s collection. In comparing Exhibit 1019 to

Appendix CHIANG04, it is my determination that Exhibit 1019 is a true and correct copy of "Kinetics of a naltrexone sustained-release preparation" by C.N. Chiang, et al. as published in Clinical Pharmacology and Therapeutics.

44. The 008 field of the MARC record in Appendix CHIANG03 indicates the date of record creation. The 008 field of Appendix CHIANG03 indicates the Penn State University Library first acquired their database access to Clinical Pharmacology and Therapeutics as of November 28, 2000. Considering this information, it is my determination that Clinical Pharmacology and Therapeutics November 1984 and therefore "Kinetics of a naltrexone sustained-release preparation" was made available to the public via the Penn State University Library shortly after November 28, 2000 and likely earlier via its initial publication in November 1984.

45. I have reviewed Exhibit 1020, "Pharmacokinetic Quantitation of Naltrexone Release From Several Sustained-Release Delivery Systems" by R.H. Reuning, et al as published in NIDA Research Monograph 28 (1981).

46. Attached hereto as Appendix REUNING01 is a true and correct copy of the MARC record for NIDA Research Monograph as held by the University at Buffalo Library. I secured this record myself from the library's public catalog. The MARC record contained within Appendix REUNING01 accurately describes the title, publisher and ISSN number of NIDA Research Monograph. The Locations

field present on page 2 of this record indicates the library's collection includes the 28 (1981) issue of NIDA Research Monograph containing "Pharmacokinetic Quantitation of Naltrexone Release From Several Sustained-Release Delivery Systems". In comparing Exhibit 1020 to Appendix REUNING01, it is my determination that Exhibit 1020 is a true and correct copy of "Pharmacokinetic Quantitation of Naltrexone Release From Several Sustained-Release Delivery Systems" by R.H. Reuning, et al as published in NIDA Research Monograph.

The 008 field of the MARC record in Appendix REUNING01 indicates the date of record creation. The 008 field of Appendix REUNING01 indicates the University at Buffalo Library first acquired their collection of NIDA Research Monograph as of July 27, 1988. Considering this information, it is my determination that NIDA Research Monograph 28 (1981) and therefore "Pharmacokinetic Quantitation of Naltrexone Release From Several Sustained-Release Delivery Systems" was made available to the public via the University at Buffalo Library shortly after July 27, 1988 and likely earlier via its initial publication in 1981.

47. I have been retained on behalf of the Petitioner to provide assistance in the above-illustrated matter in establishing the authenticity and public availability of the documents discussed in this declaration. I am being compensated for my services in this matter at the rate of \$200.00 per hour plus reasonable expenses. My statements are objective, and my compensation does not depend on the outcome of this matter.

48. In signing this Declaration, I understand that the Declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in the case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

49. I declare under penalty of perjury that the foregoing is true and correct.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: 1/24/2025

A handwritten signature in black ink, appearing to read 'June Ann Munford', with a stylized flourish at the end.

June Ann Munford

Appendix CV

June A. Munford
Curriculum Vitae

Education

University of Wisconsin-Milwaukee - MS, Library & Information Science, 2009
Milwaukee, WI

- Coursework included cataloging, metadata, data analysis, library systems, management strategies and collection development.
- Specialized in library advocacy, cataloging and public administration.

Grand Valley State University - BA, English Language & Literature, 2008
Allendale, MI

- Coursework included linguistics, documentation and literary analysis.
- Minor in political science with a focus in local-level economics and government.

Professional Experience

Researcher / Expert Witness, October 2017 – present
Freelance ● Pittsburgh, Pennsylvania & Grand Rapids, Michigan

- Material authentication and public accessibility determination. Declarations of authenticity and/or public accessibility provided upon research completion. Experienced with appeals and deposition process.
- Research provided on topics of public library operations, material publication history, digital database services and legacy web resources.
- Past clients include Alston & Bird, Arnold & Porter, Baker Botts, Fish & Richardson, Erise IP, Irell & Manella, O'Melveny & Myers, Perkins-Coie, Pillsbury Winthrop Shaw Pittman and Slayden Grubert Beard.

Library Director, February 2013 - March 2015
Dowagiac District Library ● Dowagiac, Michigan

- Executive administrator of the Dowagiac District Library. Located in

Southwest Michigan, this library has a service area of 13,000, an annual operating budget of over \$400,000 and total assets of approximately \$1,300,000.

- Developed careful budgeting guidelines to produce a 15% surplus during the 2013-2014 & 2014-2015 fiscal years while being audited.
- Using this budget surplus, oversaw significant library investments including the purchase of property for a future building site, demolition of existing buildings and building renovation projects on the current facility.
- Led the organization and digitization of the library's archival records.
- Served as the public representative for the library, developing business relationships with local school, museum and tribal government entities.
- Developed an objective-based analysis system for measuring library services - including a full collection analysis of the library's 50,000+ circulating items and their records.

November 2010 - January 2013

Librarian & Branch Manager, Anchorage Public Library ● Anchorage, Alaska

- Headed the 2013 Anchorage Reads community reading campaign including event planning, staging public performances and creating marketing materials for mass distribution.
- Co-led the social media department of the library's marketing team, drafting social media guidelines, creating original content and instituting long-term planning via content calendars.
- Developed business relationships with The Boys & Girls Club, Anchorage School District and the US Army to establish summer reading programs for children.

June 2004 - September 2005, September 2006 - October 2013

Library Assistant, Hart Area Public Library
Hart, MI

- Responsible for verifying imported MARC records and original MARC

cataloging for the local-level collection as well as the Michigan Electronic Library.

- Handled OCLC Worldcat interlibrary loan requests & fulfillment via ongoing communication with lending libraries.

Professional Involvement

Alaska Library Association - Anchorage Chapter

- Treasurer, 2012

Library Of Michigan

- Level VII Certification, 2008
- Level II Certification, 2013

Michigan Library Association Annual Conference 2014

- New Directors Conference Panel Member

Southwest Michigan Library Cooperative

- Represented the Dowagiac District Library, 2013-2015

Professional Development

Library Of Michigan Beginning Workshop, May 2008

Petoskey, MI

- Received training in cataloging, local history, collection management, children's literacy and reference service.

Public Library Association Intensive Library Management Training, October 2011

Nashville, TN

- Attended a five-day workshop focused on strategic planning, staff management, statistical analysis, collections and cataloging theory.

Alaska Library Association Annual Conference 2012 - Fairbanks, February 2012

Fairbanks, AK

- Attended seminars on EBSCO advanced search methods, budgeting, cataloging, database usage and marketing.

Depositions

2019 ● Fish & Richardson

Apple v. Qualcomm (IPR2018-001281, 39521-00421IP, IPR2018-01282 and 39521-00421IP2)

2019 ● Erise IP

Implicit, LLC v. Netscout Systems, Inc (Civil Action No. 2:18-cv-53-JRG)

2019 ● Perkins-Coie

Adobe Inc. v. RAH Color Technologies LLC (Cases IPR2019-00627, IPR2019-00628, IPR2019-00629 and IPR2019-00646)

2020 ● O'Melveny & Myers

Maxell, Ltd. v. Apple Inc. (Case No. 5:19-cv-00036-RWS)

2021 ● Pillsbury Winthrop Shaw Pittman LLP

Intel v. SRC (IPR2020-1449)

2022 ● Perkins-Coie

Realtek v. Future Link (IPR2021-01182)

2023 ● Fish & Richardson

Neuroderm Ltd. v. Abbvie, Inc (Case No. PGR2022-00040)

2023 ● Fish & Richardson

Nearmap US Inc. v. Pictometry International Corp. (IPR2022-00735)

2023 ● Fish & Richardson

Samsung Electronics v. MemoryWeb LLC (Case No. 39843-0136PS1)

2023 ● Pillsbury Winthrop Shaw Whitman LLP

Gravel Rating Systems v. Costco Wholesale Corp. (Civil Action No. 4:21-cv-149-ALM)

2024 ● Willkie-Farr

Netflix, Inc. v. VideoLabs. Inc. (IPR2023-00628)

Limited Case and Clientele History

Alston & Bird

- Ericsson

v. Collision Communications (IPR2022-01233)

- Nokia

v. Neptune Subsea, Xtera (Case No. 1:17-cv-01876)

- Universal Electronics Inc

v. Roku Inc (IPR2022-00818)

Arnold & Porter

- Ivantis

v. Glaukos (Case No. 8:18-cv-00620)

- Samsung

v. Jawbone (Case No. 2:21-cv-00186)

Benesch Friedlander Coplan & Aronoff

- Voyis
 - v. Cathx (Case No. 5:21-cv-00077-RWS)

Deschert LLP

- Smaxtec Animal Care
 - v. ST Reproductive Technologies, LLC (IPR2024-00885)

Erise I.P.

- Apple
 - v. Ericsson Inc. (IPR2022-00715)
 - v. Future Link Systems (IPRs 6317804, 6622108, 6807505, and 7917680)
 - v. INVT (Case No. 20-1881)
 - v. Navblazer LLC (IPR2020-01253)
 - v. Qualcomm (IPR2018-001281, 39521-00421IP, IPR2018-01282, 39521-00421IP2)
 - v. Quest Nettech Corp (Case No. 2:19-cv-00118-JRG)
 - v. Telefonaktiebolaget LM Ericsson (IPR2022-00275)
 - v. Theta IP, LLC (IPR2024-00818)

- Fanduel
 - v. CGT (Case No. 19-1393)

- Garmin
 - v. Phillips North America LLC (Case No. 2:19-cv-6301-AB-KS)

- Netscout

- v. Longhorn HD LLC (Case No. 2:20-cv-00349)

- v. Implicit, LLC (Civil Action No. 2:18-cv-53-JRG)

- Sony Interactive Entertainment LLC

- v. Bot M8 LLC (IPR2020-01288)

- v. Infernal Technology LLC (Case No. 2:19-CV-00248-JRG)

- Unified Patents

- v. GE Video Compression (Civil Action No. 2:19-cv-248)

Fish & Richardson

- Apple

- v. AliveCor (3:21-cv-03958)

- v. LBS Innovations (Case No. 2:19-cv-00119-JRG-RSP)

- v. Koss Corporation (IPR2021-00305)

- v. Masimo (IPR 50095-0012IP1, 50095-0012IP2, 50095-0013IP1, 50095-0013IP2, 50095-0006IP1, 50095-0135IP1)

- v. Neonode (Case No. 21-cv-08872-EMC)

- v. Qualcomm (IPR2018-001281, 39521-00421IP, IPR2018-01282, 39521-00421IP2)

- Dell

- v. Neo Wireless (IPR2022-00616)

- Dish Network

- v. Entropic Communications, LLC (Case No. 2:2023-CV-01043)

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v. TQ Delta LLC (Case No. 18-1798)

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- Genetec

v. Sensormatic Electronics (Case No. 1:20-CV-00760)

- Huawei

v. Bell Northern Research LLC (IPR2019-01174)

- Kianxis

v. Blue Yonder (Case No. 3:20-cv-03636)

- LG Electronics

v. Bell Northern Research LLC (Case No. 3:18-cv-2864-CAB-BLM)

- Metaswitch

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- Microsoft

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- Mom Enterprises

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- Nearmap Inc

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- Neuroderm Ltd.

v. Abbvie, Inc (Case No. PGR2022-00040)

- Realtek Semiconductor

v. Future Link (IPR2021-01182)

- Quectel

v. Koninklijke Philips (Case No. 1:20-cv-01710)

- Samsung

v. Aire Technology (IPR2022-00877)

v. Bell Northern Research (Case No. 2:19-cv-00286-JRG)

v. Communication Technologies Inc (IPR2022-01221)

v. Jawbone Innovations (IPR2022-00865)

v. MemoryWeb LLC (IPR2022-00885)

v. Dodots Licensing Solutions (IPR2023-00701)

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- Texas Instruments

v. Vantage Micro LLC (IPR2020-01261)

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 - v. BitMICRO (Case No. 5:23-cv-00625)
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- Realtek Semiconductor
 - v. Future Link (IPR2021-01182)
- Twitter Inc
 - v. VOIP-Pal.com (Case No. 3:20-cv-02397-JD)
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EXHIBIT 1004

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Depot naltrexone: long-lasting antagonism of the effects of heroin in humans

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Abstract *Rationale:* Naltrexone, an opioid antagonist, is currently approved as a treatment for heroin dependence. However, naltrexone is generally not well accepted by patients, and medication non-compliance is a difficult obstacle to treatment. A sustained-release form of naltrexone may improve compliance. *Objective:* The present study was designed to evaluate the time course, safety, and effectiveness of a depot formulation of naltrexone (Depotrex®). *Methods:* Twelve heroin-dependent individuals participated in an 8-week inpatient study. After a 1-week detoxification period, six participants received 192 mg naltrexone base and six participants received 384 mg naltrexone base. For safety, the low dose of depot naltrexone was tested before the high dose. The effects of heroin (0, 6.25, 12.5, 18.75, 25 mg, IV) were evaluated for the next 6 weeks. One dose of heroin was tested per day on Mondays through Fridays, and the entire dose range was tested each week. Active heroin doses were administered in ascending order during the week, while placebo could be administered on any day. Subjective, performance, and physiological effects were measured both before and after heroin administration. The hypotheses were that depot naltrexone would antagonize the effects of heroin, and that the high dose of depot naltrexone would produce a more effective and longer-lasting antagonism than the low dose. *Results:* The low and high doses of depot naltrexone antagonized heroin-induced subjective ratings for 3 and 5 weeks, respectively. Plasma levels of naltrexone remained above 1 ng/ml for approximately 3 and 4 weeks after administration of 192 mg and 384 mg naltrexone. Other than the initial discomfort associated with the injection of depot

naltrexone, there were no untoward side-effects. *Conclusions:* These results suggest that this depot formulation of naltrexone provides a safe, effective, long-lasting antagonism of the effects of heroin.

Keywords Heroin · Human · Naltrexone · Opioid · Subjective effect · Sustained-release · Depotrex

Introduction

Naltrexone, an orally effective opioid antagonist, was approved in 1984 by the Food and Drug Administration as a maintenance medication for the treatment of heroin dependence. Naltrexone potently antagonizes the effects of opioid agonists, while producing no agonist effects of its own (Jaffe and Martin 1990). Tolerance does not develop to naltrexone's antagonist effects and the drug has few side effects, even after chronic administration of over 1 year (Kleber et al. 1985). Because of its ability to antagonize the effects of mu opioid agonists, its long duration of action, and its favorable pharmacokinetic and metabolic characteristics (Martin et al. 1966, 1973), naltrexone initially held great promise as a treatment for opioid dependence. The early rationale for using a pure antagonist was that once the individual was maintained on naltrexone, subsequent attempts to self-administer the illicit opioid would not produce euphoria (Wikler 1965; Martin et al. 1966) and the user would eventually discontinue opioid use altogether.

Although the use of naltrexone as a maintenance therapy for opioid abuse can be effective (Martin et al. 1973; O'Brien et al. 1975; Judson et al. 1981), it has been used most successfully with only a select subpopulation of highly motivated individuals. Because of the problems with medication non-compliance, naltrexone therapy has not lived up to its initial promise. This may be in part because opioid users are accustomed to self-administering potent reinforcers, and, by contrast, the complete absence of opioid-induced reinforcing effects may be unacceptable. Another factor that may contribute to noncom-

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Table 1 Participant demographics. Numbers in parentheses represent ± 1 SEM

	192 mg naltrexone	384 mg naltrexone
Age (average; years)	33.8 (2.5)	29.2 (3.2)
Years of heroin use (average)	10.7 (2.5)	9.1 (3.5)
Amount spent for heroin (average; \$/day)	\$39 (4)	\$55 (12)
Tobacco cigarette use (range; no. per day)	8–20	10–20
Cocaine use (range; occasions/week)	0–1	0–3
Amphetamine use (range; occasions/week)	0–1	0
Marijuana use (range; occasions/week)	0–1	0–3
Alcohol use (range; occasions/week)	0–1	0–3
Sedative use (range; occasions/week)	0–1	0–1

pliance is that, unlike methadone, discontinuation of naltrexone maintenance has no adverse consequences (e.g. withdrawal effects). Furthermore, naltrexone itself may induce adverse neuropsychiatric and gastrointestinal effects, such as dysphoria, nausea, and abdominal pain (Hollister et al. 1981; Crowley et al. 1985; Oncken et al. 2001).

Sustained-release forms of naltrexone could increase compliance and ultimately improve treatment effectiveness (Martin and Sandquist 1974; Abrahams and Ronel 1975; Chiang et al. 1985a, 1985b). Chiang et al. (1985a, 1985b), for example, administered biodegradable beads containing a dose of 63 mg naltrexone to normal, healthy volunteers. Following an initial burst of release, this formulation yielded relatively constant plasma levels of naltrexone (0.3–0.5 ng/ml) for up to 1 month. However, when these investigators administered challenge doses of morphine (15 mg IM), the results were variable. In some participants, morphine was completely ineffective, while in others, morphine-like effects were observed. In addition, three of the five participants who completed the study developed tissue inflammation near the site of bead implantation (Chiang et al. 1985b). Although the adverse tissue reaction and the variable antagonist effectiveness of the naltrexone beads limited its clinical utility, the rationale behind the development of a sustained-release form of naltrexone was sound.

A new depot formulation of naltrexone (Depotrex®) has been developed that provides a stable, long-lasting elevation in plasma naltrexone levels with either no or minimal side-effects (Heishman et al. 1994; Alim et al. 1995; Kranzler et al. 1998). In an early tolerability study, Alim and colleagues (1995) reported blockade of the physiological and subjective effects of 10 mg intravenous (IV) morphine in cocaine-dependent participants who received 206 mg depot naltrexone; side-effects associated with naltrexone were minimal in these participants. Kranzler and colleagues (1998) further showed that 206 mg depot naltrexone significantly reduced the percentage of heavy drinking days in alcoholics. Adverse effects reported after depot naltrexone were comparable to those reported after oral naltrexone administration. Although this formulation of depot naltrexone appears to be safe and effective in treating alcohol dependence, it has not yet been tested with heroin. The purpose of the current study was 1) to determine whether the new formulation of depot naltrexone will antagonize the effects

of heroin at doses comparable to those used on the streets today, and 2) to assess the duration of antagonist effect of 192 mg and 384 mg depot naltrexone. The hypothesis was that depot naltrexone would dose-dependently antagonize the effects of heroin.

Materials and methods

Participants

Fifteen heroin-dependent men, who were not seeking treatment for their drug use, began the 8-week protocol. Three participants left the study prior to depot naltrexone administration: one was discharged for aggressive behavior toward the staff, and two left for personal reasons. Twelve participants (eight non-Hispanic Caucasian, three Hispanic, and one African American) completed the study: six received 192 mg depot naltrexone, and six received 384 mg depot naltrexone (Table 1). The low dose of depot naltrexone was tested in the first six participants. The groups did not differ in age, years of heroin use, and amount of money spent on heroin per day. All participants had experience using heroin IV. One participant in the low-dose group and two in the high-dose group preferred to use heroin intranasally; all other participants preferred to use heroin IV. All participants were dependent on heroin at the start of the study, as verified by a naloxone challenge test (Wang 1974).

After an initial telephone interview, eligible participants completed detailed questionnaires on drug use, general health and medical history, and a medical and psychological evaluation in the laboratory. An electrocardiogram and Mantoux test or chest X-ray were also performed. Routine laboratory analyses included a blood chemistry panel, thyroid function test, syphilis and hepatitis (A, B, and C) screening, and urinalysis. Urine drug toxicologies (opioids, cocaine, benzodiazepines, cannabinoids, and amphetamines) were also performed using a radiative energy attenuation and fluorescence polarization immunoassay system (AD_x System; Abbott Laboratories, Abbott Park, Ill., USA). Participants were told that they would be detoxified from heroin during the first week of the study, that they would receive one of two doses of a depot formulation of naltrexone, and that a range of IV heroin doses would be tested each week for the 6 weeks following depot naltrexone administration.

Participants were excluded from the study if they were seeking drug treatment, dependent on alcohol or illicit drugs other than opioids, or had a major Axis I psychiatric diagnosis other than opioid dependence. Those who had recent histories of violence or who were on parole/probation were excluded from the study. Participants were required to be physically healthy, and fully able to perform all study procedures. Although both men and women were screened for the study, none of the women met the eligibility requirements. Prior to admission, participants completed a training session, during which the study procedures were explained to them in detail. Volunteers were paid \$25 per inpatient day and an additional \$25 per day bonus if they completed the study. Participants signed consent forms describing the aims of the study, and

the potential risks and benefits of participation. Free HIV testing and education were offered, and during the last week of the study, participants were offered referrals for treatment. This study was approved by the Institutional Review Board of the New York State Psychiatric Institute (NYSPI).

Apparatus

During experimental sessions, participants were seated in a room equipped with Macintosh computers. All computer activities, vital signs and behaviors were continuously monitored by the experimenters in an adjacent control room via a continuous on-line computer network, video cameras, and vital signs monitors (cardiovascular function was measured using a Sentry II Vital Signs Monitor, NBS Medical, Costa Mesa, Calif., USA; arterial oxygen saturation was measured using a pulse oximeter Model 400, Palco Laboratories, Santa Cruz, Calif., USA). Communication between the staff and participants was kept to a minimum during experimental sessions.

Detoxification procedures

Participants were admitted into the hospital, and detoxified during the first week after admission. Buprenorphine (8 mg sublingual tablet; National Institute on Drug Abuse, Rockville, Md., USA) was administered on the first 1–2 days after admission. Two days after the last buprenorphine dose, oral naltrexone (DuPont Pharma, Wilmington, Del., USA) was administered for 3 consecutive days (25, 50, and 50 mg per day) to ensure that participants were willing and able to tolerate its effects. Clonidine HCl (0.2 mg PO, every 6 h; Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Conn., USA), ketorolac tromethamine (30 mg IM, every 6 h; Roche Laboratories, Nutley, N.J., USA), prochlorperazine (10 mg PO or IM, every 8 h; SmithKline Beecham Consumer Healthcare, Pittsburgh, Penn., USA) and clonazepam (2 mg PO, every 8 h; Roche Laboratories) were available, as needed, during the detoxification week. Thereafter, trazodone (50–100 mg PO, at bedtime; Warner Chilcott, Morris Plains, N.J., USA) was available if participants reported having trouble sleeping. Depot naltrexone was administered on a Monday morning, 2 days after the last oral naltrexone dose.

General procedures

The effects of IV heroin (placebo, 6.25, 12.5, 18.75, and 25 mg) were evaluated each week for 6 weeks following depot naltrexone administration. The entire dose range was tested each week, and one dose of heroin was tested each day on weekdays. For safety, active heroin doses were administered in ascending order within each week, with the exception that the day of placebo injection was varied across weeks. On the day that depot naltrexone was administered, placebo was tested during the experimental session.

Experimental sessions

During all sessions, participants completed computerized tasks and subjective-effects questionnaires. Heart rate and blood pressure were measured every 2 min, and blood oxygen saturation was monitored continuously with a pulse oximeter and recorded every minute during experimental sessions. Participants received breakfast between 0800 and 0900 and lunch between 1230 and 1330 hours. Experimental sessions occurred between 0930 and 1130 hours. Participants were not allowed to smoke tobacco cigarettes during experimental sessions.

Physiologic, subjective and performance effects were measured both before and after drug administration (see descriptions below). Heroin or placebo was administered only if vital signs were within safe limits ($\text{SpO}_2 > 93\%$). A photograph was taken of the right pupil before and 4, 10, 20, 40 and 60 min after drug ad-

ministration. The subjective-effects battery (see description below) was administered before and 4, 40 and 90 min after drug administration. The performance battery (see description below) was administered before and 10 and 60 min after drug administration. The Subjective Opioid Withdrawal Scale was administered before drug administration. The Drug Effects Questionnaire was administered 90 min after drug administration.

Subjective measures

Four questionnaires were used to assess subjective effects throughout the experimental sessions. The first questionnaire was a 26-item visual analog scale (VAS) designed to assess subjective and physiological effects (modified from Foltin and Fischman 1995). The first 18 lines were labeled with adjectives describing mood states (e.g., "I feel..." "high") and four additional lines, labeled with questions about the dose just received (i.e. "I liked the dose," "For this dose, I would pay"). Participants also indicated, by making a mark along a 100 mm line, how much they "wanted" each of the following drugs: heroin, cocaine, alcohol, and tobacco. Participants rated each item on the VAS from "Not at all" (0 mm) to "Extremely" (100 mm), except for the "For this dose, I would pay" question, which ranged between \$0 (0 mm) to \$20 (100 mm). The second questionnaire was a 13-item opioid symptom checklist consisting of true/false questions designed to measure opioid effects (e.g. "My skin is itchy," etc.; Fraser et al. 1961; Foltin and Fischman 1992). The VAS and opioid symptom checklist together constituted the subjective-effects battery. The third questionnaire was the 16-item Subjective Opioid Withdrawal Scale (SOWS; Handelsman et al. 1987). Participants rated each item on a scale from 0 to 4, with 0 being "Not at all" and 4 being "Extremely" (e.g. "I have gooseflesh," etc.). The fourth questionnaire was a 6-item Drug Effects Questionnaire (DEQ; Evans et al. 1995). Participants described drug effects by selecting among a series of possible answers ranging from 0 ("No effects at all") to 4 ("Very strong (good, bad, etc.) effects"). Ratings of drug liking ranged between -4 ("Dislike very much") to 4 ("Like very much").

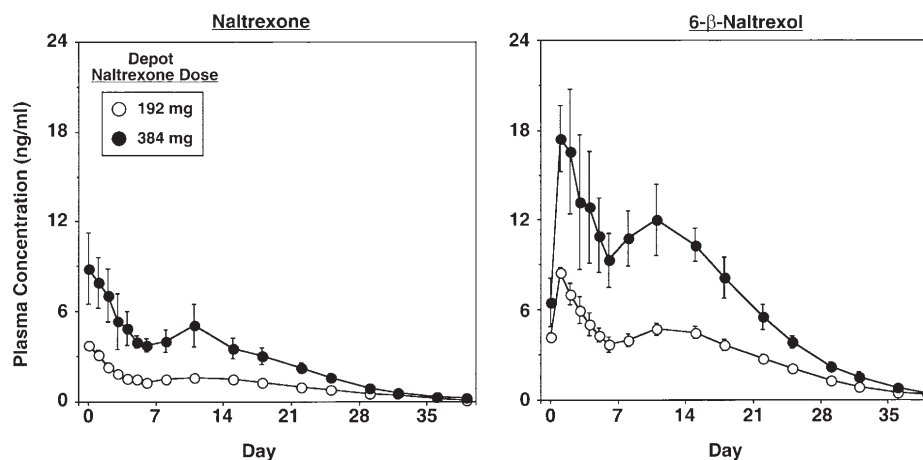
Task battery

The task battery consisted of four tasks: the first task was a 3-min digit-symbol substitution task, during which participants were required to emulate a series of patterns on a keypad (McLeod et al. 1982). The second task was a 10-min divided attention task, which consisted of concurrent pursuit-tracking and vigilance tasks (Miller et al. 1988). The third task was a 10-min rapid information processing task, during which a series of digits was displayed rapidly on the computer screen (100 digits/min), and participants were instructed to press a key as quickly as possible after three consecutive odd or even digits (Wesnes and Warburton 1983). The fourth task was a 3-min repeated acquisition of response sequences task, during which four buttons were illuminated, and participants were instructed to learn a ten-response sequence of button presses (Kelly et al. 1993).

Physiological measures

A blood pressure cuff was attached to the non-dominant arm, which recorded automatically every 2 min. Participants were also connected to a pulse oximeter via a soft sensor on a finger of the dominant hand, which monitored arterial blood oxygen saturation ($\%\text{SpO}_2$). For safety, supplemental oxygen (2 l/min) was provided via a nasal cannula during all experimental sessions. A specially modified Polaroid camera with a close-up lens ($\times 2$ magnification) was used to take pupil photographs. All photographs were taken under ambient lighting conditions. Horizontal and vertical measurements of pupil diameter were made using calipers, and then these two measurements were averaged and divided by 2 to correct for the $\times 2$ magnification.

Fig. 1 Mean plasma levels of naltrexone (*left panel*) and 6- β -naltrexol (*right panel*) as a function of depot naltrexone dose and days after administration of depot naltrexone. Data points represent the mean across 6 participants per group. Error bars represent ± 1 SEM



Blood was drawn 2 h, 1, 2, 3, 4, 5, 6, 8, 11, 15, 18, 22, 25, 29, 32, 36, and 39 days after administration of depot naltrexone, and immediately centrifuged at 3000 rpm for 15 min. Plasma was drawn off and stored at -20°C until it was shipped by overnight mail on dry ice for analyses of naltrexone and 6- β -naltrexol (Center for Human Toxicology, University of Utah, Salt Lake City, Utah, USA). Analyses were performed by solid phase extraction and negative ion chemical ionization gas chromatography/mass spectrometry, as described by Huang and colleagues (1997). The lower limit of detectability for both analytes was 0.1 ng/ml.

Blood was also drawn prior to, and at weekly intervals after administration of depot naltrexone for analyses of liver enzymes (AST, ALT, GGT).

Drugs

Depot naltrexone (Depotrex[®]) was manufactured by Biotek Inc. (Woburn, Mass., USA) and provided by the National Institute on Drug Abuse. Depotrex is a registered trademark of Biotek, Inc. Naltrexone microcapsules and placebo microspheres were packaged in sterile single-dose vials. After reconstituting in suspending medium, 2.4 ml of the suspension was injected. The active formulation contained drug equivalent to 192 mg naltrexone base. The placebo formulation contained the equivalent weight in polymer microspheres. Injections were administered subcutaneously into the buttocks (one injection per buttock), using an 18 gauge needle. For the low dose, participants received one placebo and one naltrexone injection (192 mg naltrexone base), and for the high dose, participants received two naltrexone injections (394 mg naltrexone base). For safety, the low dose of Depotrex was tested in the first six participants, and the high dose of Depotrex was tested in the next six participants.

Heroin HCl was provided by the National Institutes on Drug Abuse and prepared by the Columbia-Presbyterian Medical Center research pharmacy. A 25 mg/ml heroin concentration was prepared in a 5% dextrose solution to enhance stability. Dose calculations were based on the hydrochloride salt form. Heroin was stored in a freezer and used within 3 months of preparation. The stock solution was diluted in 5% dextrose to produce each dose. Placebo (5% dextrose solution) or heroin (6.25, 12.5, 18.75, and 25 mg) was administered intravenously over a 30-s period in a total volume of 2 ml. Heroin doses were administered in a double-blind fashion. Physiological saline solution was infused continuously during experimental sessions, except during drug administration. Between 1 and 2 ml heparinized saline (10 IU/ml) was flushed into the catheter four to eight times each day. All venous catheters were maintained as heparin locks and were removed within 72 h of insertion.

Supplemental medications available to all participants for the duration of the study included: Mylanta, acetaminophen, ibuprofen, Colace, Milk of Magnesia and multi-vitamins with iron.

Morning urine samples were collected daily and one random sample per week was screened for the presence of other illicit substances. No illicit substances were found in the participants' urine samples.

Statistical analyses

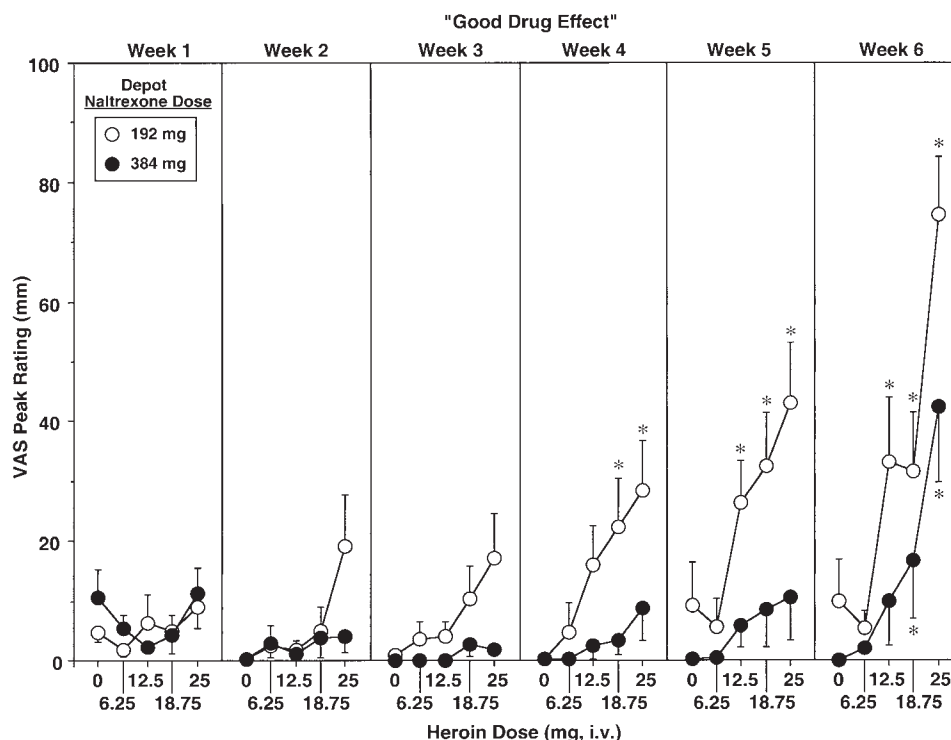
Repeated-measures analyses of variance (ANOVA) with planned comparisons were used to address the following questions: 1) What was the duration of antagonism of heroin's effects? 2) Did the low and high doses of depot naltrexone differ in ability to antagonize the effects of heroin? In order to address the first question, the data for each group were analyzed separately as a function of week (1–6) and heroin dose (0, 6.25, 12.5, 18.75, 25 mg). Twenty-five planned comparisons were made: each week (2–6) was compared to week 1 for each dose (e.g. placebo-week 2 versus placebo-week 1, placebo-week 3 versus placebo-week 1, placebo-week 4 versus placebo-week 1, etc.) because it was likely that virtually complete antagonism would occur during week 1. In order to address the second question, an overall analysis was performed with one between-group factor (group) and two within-group factors (week, heroin dose): the main effect of group, and the week $\times$ group and dose $\times$ group effects were evaluated. Interaction effects were examined using post-hoc comparisons. Peak subjective ratings, peak performance effects, trough pupil diameter, liver enzyme levels, average arterial oxygen saturation, and plasma levels of naltrexone and 6- β -naltrexol were analyzed. Liver enzymes (AST, ALT, GGT) were also analyzed: each week post-depot naltrexone was compared to a pre-depot naltrexone baseline. Due to an excessive number of missing data points, the cardiovascular data were not analyzed. To control for type I errors, a modified Bonferroni test was used in that only those comparisons with $P < 0.01$ were considered statistically significant.

Results

Plasma drug levels

Figure 1 shows mean plasma levels of naltrexone (left panel) and 6- β -naltrexol (right panel) for each group as a function of time since the depot naltrexone injection. Two hours after administration of 192 mg and 384 mg depot naltrexone, plasma levels of naltrexone were 3.8 (± 0.2) and 8.9 (± 1.4) ng/ml. Plasma levels of 6- β -naltrexol were 8.5 (± 0.3) and 17.4 (± 1.3) ng/ml, respectively, 24 h after administration of 192 mg and 384 mg depot naltrexone. Across individual participants, plasma levels

Fig. 2 Mean peak VAS ratings of "Good Drug Effect" after administration of heroin (0–25 mg) as a function of depot naltrexone dose and study week (week 1: *left panel*; week 6: *right panel*). Maximum rating=100 mm. Data points represent mean peak ratings ($n=6$ per group). Error bars represent ± 1 SEM. * Indicates significant differences from week 1



of naltrexone ranged between 3.1 and 4.5 ng/ml after administration of 192 mg depot naltrexone, and 5.6 and 14.2 ng/ml after administration of 384 mg depot naltrexone. After administration of 192 mg and 384 mg of depot naltrexone, plasma levels of naltrexone were less than 1 ng/ml on day 22 and 29, respectively. The group and group $\times$ day effects for naltrexone [group: $F(1,10)=48.5$, $P<0.0001$; group $\times$ day: $F(1,10)=8.6$, $P<0.0001$] and 6- β -naltrexol [group: $F(1,10)=33.8$, $P<0.0002$; group $\times$ day: $F(1,10)=8.3$, $P<0.0001$] were significant.

Subjective effects

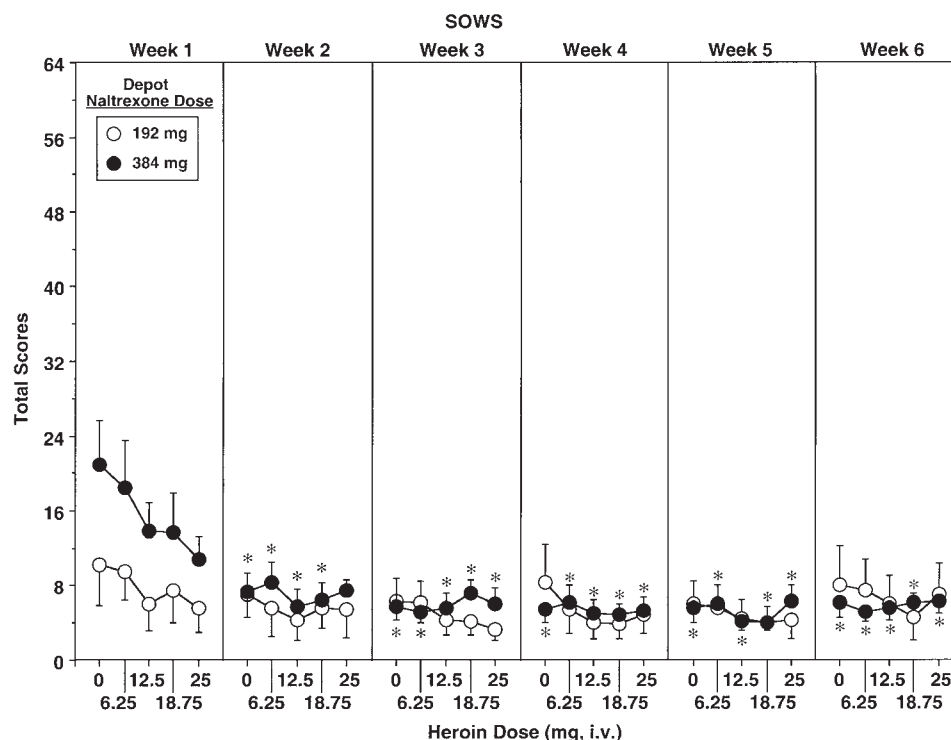
Figure 2 shows mean peak visual analog scale ratings of "Good Drug Effect" for each group as a function of heroin dose and week. After low-dose depot naltrexone, ratings of "Good Drug Effect" significantly increased by week 4, relative to week 1, after administration of 18.75 mg [$F(1,100)=6.4$, $P<0.01$] and 25 mg heroin [$F(1,100)=7.9$, $P<0.006$]; ratings of "Good Drug Effect" significantly increased by week 5 after administration of 12.5 mg heroin [$F(1,100)=8.4$, $P<0.004$]. In the high-dose group, ratings of "Good Drug Effect" did not significantly increase until week 6, after 18.75 mg [$F(1,100)=7.5$, $P<0.007$] and 25 mg heroin [$F(1,100)=47.3$, $P<0.0001$]. Both the week $\times$ group [$F(5,50)=4.8$, $P<0.001$] and dose $\times$ group [$F(4,40)=4.4$, $P<0.005$] effects were significant for ratings of "Good Drug Effect." Several other VAS ratings showed a similar pattern including ratings of "High," "Liking," drug "Potency," drug "Quality," and how much they would be willing to pay for the dose (data not shown). The dose $\times$ group

effect was significant [$F(4,40)=4.2$, $P<0.006$], and the week $\times$ group effect approached statistical significance [$F(5,50)=2.9$, $P<0.02$] for ratings of "High." Although ratings tended to be higher in the low-dose group for VAS ratings of "Liking," drug "Potency," and drug "Quality," the week $\times$ group and dose $\times$ group effects were not statistically significant for these items.

VAS ratings of "I feel..." "Gooseflesh," "Depressed," "Muscle Pain," "Anxious," and "Restless" were elevated in both groups during the first week after receiving depot naltrexone, and were higher in the high-dose group (data not shown). The week $\times$ group effect was statistically significant for ratings of "Gooseflesh" [$F(5,50)=3.4$, $P<0.01$] and "Depressed" [$F(5,50)=3.5$, $P<0.009$], while the week $\times$ group effect for ratings of "Muscle Pain" ($P<0.03$), "Anxious" ($P<0.04$), and "Restless" ($P<0.04$) approached statistical significance. Ratings of "I Want Heroin," which did not vary across study weeks or heroin doses, were significantly elevated in the high-dose group [main effect of group: $F(1,10)=26.3$, $P<0.0004$]. Ratings of "I Want Heroin" ranged between 26 and 37 in the low-dose group, and 86 and 95 in the high-dose group.

The pattern of results obtained from the opioid symptom checklist and DEQ (data not shown) were similar to the VAS ratings of "Good Drug Effect" (Fig. 2) in that total scores on the opioid symptom checklist and DEQ ratings of drug "Liking," "Good Drug Effect," strength of drug effect, and desire to take the drug again increased as a function of heroin dose and across study weeks. The week $\times$ group effect was statistically significant for the opioid symptom checklist [$F(5,50)=3.2$, $P<0.01$]. Although ratings tended to be higher in the

Fig. 3 Mean total scores on the Subjective Opioid Withdrawal Scale (SOWS) after administration of heroin as a function of depot naltrexone dose and study week. Maximum score=64. All other details are as in Fig. 2



low-dose group compared to the high-dose group, the week $\times$ group and dose $\times$ group effects were not statistically significant for any of the items on the DEQ.

Subjective ratings of opioid withdrawal, as measured by total scores on the SOWS, did not significantly differ between groups during detoxification, prior to administration of depot naltrexone. SOWS scores peaked on day 4 after admission: total SOWS scores on day 4 of withdrawal were 22.5 ($\pm$ 11.2) and 26.3 ($\pm$ 7.3), out of a maximum possible score of 64, after administration of 192 and 384 mg depot naltrexone, respectively. On the day prior to administration of depot naltrexone, SOWS scores were 11.0 ($\pm$ 8.2) and 18.7 ($\pm$ 9.0) in the low- and high-dose groups, respectively. Figure 3 shows total SOWS scores after administration of depot naltrexone for each group as a function of heroin dose and week. Total SOWS scores were significantly elevated during the first week in the high-dose group, but not in the low-dose group. By the second week after administration of depot naltrexone, SOWS scores did not differ between groups. The week $\times$ group interaction for total SOWS scores approached statistical significance [$F(5,50)=2.5$, $P<0.04$].

Performance tasks

Heroin minimally affected task performance, with the exception that performance of the divided attention task was significantly impaired: in the low-dose group, the latency to identify a target significantly increased by 1.7 s during week 5, relative to week 1, after administration of 25 mg heroin [$F(1,100)=8.3$, $P<0.005$]. In the high-dose group, the latency to identify a target signifi-

cantly increased by 1.3 s during week 6, relative to week 1, after administration of 25 mg heroin [$F(1,100)=30.9$, $P<0.0001$]. Latency to identify a target did not significantly change across weeks after administration of placebo in either group. The week $\times$ group and dose $\times$ group effects were not statistically significant for latency to identify a target during the divided attention task.

Physiological effects

Figure 4 shows the effects of heroin on pupil diameter for each group as a function of heroin dose and week. During week 1, pupil diameter was large in both groups, consistent with the possibility that both groups were in mild withdrawal. After placebo administration during week 1, pupil diameter was 5.3 ($\pm$ 0.3) and 5.6 ($\pm$ 0.6) mm in the low- and high-dose groups, respectively. Pupil diameter was relatively stable under the placebo condition in both groups from weeks 2–6 (Fig. 4), although pupil diameter consistently remained larger in the high-dose group throughout the study. After administration of active doses of heroin, pupil diameter progressively decreased across study weeks in both groups. The week $\times$ group and dose $\times$ group effects were not significant for pupil diameter.

The average arterial oxygen saturation significantly decreased by 0.9% in both groups from week 1 to week 6, after administration of 25 mg heroin [low-dose group: $F(1,100)=17.2$, $P<0.0001$; high-dose group: $F(1,100)=7.8$, $P<0.006$]. However, these changes in oxygen saturation occurred in the presence of supplemental oxygen, and were not clinically significant.

Fig. 4 Mean trough pupil diameter after administration of heroin as a function of depot naltrexone dose and study week. All other details are as in Fig. 2

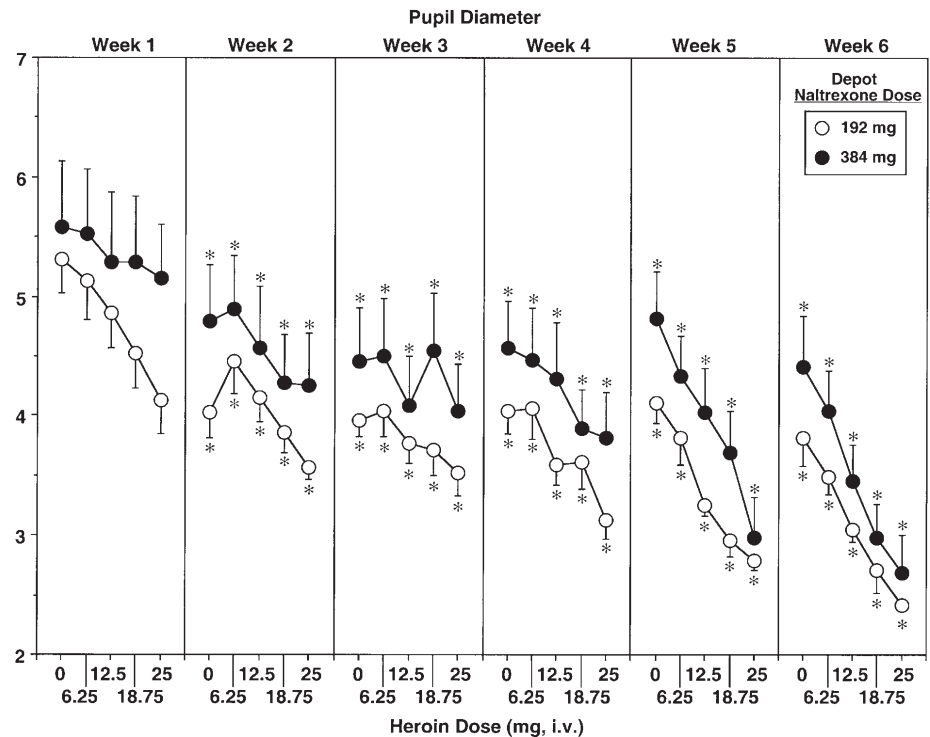


Table 2 ALT, AST, and GGT values (IU/l) at baseline and for 6 weeks following administration of 192 mg or 384 mg depot naltrexone. Numbers in parentheses represent ± 1 SEM. Asterisks represent significant differences from baseline ($P < 0.01$)

	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
192 mg							
ALT	29.2 (7.2)	54.7 (22.2)	63.3 (26.5)	65.3 (25.8)	75.2 (31.0)*	60.7 (21.4)	34.3 (6.3)
AST	19.7 (2.3)	27.8 (6.9)	31.2 (7.4)	26.8 (6.2)	34.7 (8.9)*	31.5 (7.8)	22.5 (3.1)
GGT	42.3 (17.5)	39.7 (14.6)	46.8 (14.6)	55.0 (18.4)*	62.3 (20.7)*	56.7 (18.0)*	45.7 (16.1)
384 mg							
ALT	24.3 (7.2)	132.3 (99.8)	51.8 (17.4)	45.5 (16.0)	50.0 (20.0)	53.3 (24.2)	49.0 (21.6)
AST	21.5 (3.7)	31.8 (5.9)	22.8 (4.8)	24.7 (5.5)	29.5 (6.5)	36.2 (11.8)	31.0 (6.8)
GGT	28.7 (9.7)	55.0 (24.0)	47.5 (16.4)	40.0 (11.7)	40.2 (12.1)	39.0 (11.3)	36.0 (11.3)

Liver enzyme (ALT, AST, GGT) values at baseline were within the normal range for all participants, with the exception of one individual in the low-dose group whose GGT value (128 IU/l) slightly exceeded the normal range of 5–80 IU/l. Three individuals in the low-dose group tested positive for hepatitis, and four individuals in the high-dose group tested positive for hepatitis. In the low-dose group, average GGT levels significantly increased during weeks 3, 4, and 5, relative to baseline [Tables 2; week 3: $F(1,30)=7.5$, $P<0.01$; week 4: $F(1,30)=18.6$, $P<0.0002$; week 5: $F(1,30)=9.6$, $P<0.004$]. Both ALT [$F(1,30)=7.5$, $P<0.01$] and AST [$F(1,30)=8.5$, $P<0.007$] values in the low-dose group significantly increased during week 4, relative to baseline. Although these liver enzyme values following administration of the low dose were statistically significant, it is important to note that they were not clinically significant. The increases in liver enzyme values in the low-dose group were predominantly due to one hepatitis-negative individual: his baseline

GGT value was 54 IU/l, which peaked at 226 IU/L during week 4, and returned to 54 IU/l by week 6. Liver enzyme levels did not significantly change across study weeks in the high-dose group. The non-significant, transient increase in ALT values during week 1 in the high-dose group was due to one individual who received several doses of ketorolac tromethamine during detoxification. His liver enzyme levels peaked at 630 IU/l during week 1, and returned to normal (32 IU/l) by week 3.

Side-effects

Eleven of 12 participants reported pain during administration of the depot injections. These individuals reported no discomfort while standing, and only mild discomfort at the injection sites while seated, during the first 48–72 h after the injections. There was no evidence of induration, erythema, or irritation. One participant who

inadvertently received one of the injections (placebo) intramuscularly reported pain on that side for the first 72–96 h after the injection.

Discussion

The depot formulation of naltrexone used in the current study provided a safe, effective, long-lasting antagonism of the effects of heroin. Across the time points measured, the highest naltrexone plasma levels attained after administration of 192 mg and 384 mg of depot naltrexone were $3.8 (\pm 0.2)$ and $8.9 (\pm 1.4)$ ng/ml, respectively. For comparison, Walsh et al. (1996) reported that daily administration of 50 mg oral naltrexone resulted in naltrexone plasma concentrations of approximately 30 ng/ml, while daily administration of 12.5 mg oral naltrexone resulted in naltrexone plasma concentrations of approximately 10 ng/ml (plasma samples were collected 30 min after administration of naltrexone). Therefore, the amount of drug found in plasma after depot naltrexone administration is lower than the amount found after a standard dose of naltrexone used clinically for treating heroin dependence (50 mg/day).

In the present study, antagonism of heroin's effects occurred, despite negligible plasma levels of naltrexone. An early study conducted by Vereby and colleagues (Vereby et al. 1976) showed that 100 mg oral naltrexone did not completely antagonize the effects of 25 mg IV heroin when plasma levels of naltrexone fell below approximately 2 ng/ml. In contrast, Navaratnam and colleagues (Navaratnam et al. 1994) showed that after discontinuation of day 1-day 3-day 5 dosing with 100–100–150 mg oral naltrexone, antagonism of the effects of 25 mg IV heroin continued to occur when plasma levels of naltrexone were negligible. Schuh and colleagues (Schuh et al. 1999) also demonstrated that during a "wash-out period" after discontinuation of daily administration of 100 mg oral naltrexone, antagonism of the effects of up to 4 mg IM hydromorphone continued to occur when plasma levels of naltrexone were negligible. The data presented in the current study were more consistent with those of Navaratnam et al. (1994) and Schuh et al. (1999) in that 384 mg depot naltrexone antagonized heroin-induced ratings of "I Feel High" and "I Feel a Good Drug Effect" for up to 5 weeks, even though plasma levels of naltrexone were quite low (0.3 ± 0.04 ng/ml). These data are not entirely surprising, given a previous study demonstrating that the percentage blockade of [^{11}C]carfentanil binding in the brain of normal healthy volunteers at 48, 72, 120, and 168 h after administration of 50 mg oral naltrexone was 91, 80, 46, and 30%, respectively (Lee et al. 1988). Results from the Lee et al. (1988) study suggest that orally delivered naltrexone continues to inhibit brain opioid receptors in the absence of measurable plasma levels of naltrexone. In the present experiment, it is also possible that 6- β -naltrexol, the active metabolite of naltrexone, contributed to the continued antagonism of heroin's effects, particularly

because plasma levels of this metabolite were consistently higher than naltrexone throughout the study.

In the present study, both doses of depot naltrexone initially antagonized the positive subjective effects of heroin, consistent with naltrexone's well-established effectiveness in blocking the subjective effects of opioid agonists (e.g. Altman et al. 1976; Mello et al. 1980; Preston and Bigelow 1993; Schuh et al. 1999). Although the present study clearly demonstrated a long-lasting antagonism of the subjective effects of up to 25 mg IV heroin, it did not address the question of what dose of heroin would effectively override the blockade during the first few weeks after administration of depot naltrexone. In previous studies in our laboratory, participants who were maintained on morphine reported that 25 mg heroin was roughly equivalent to one \$10 "street bag" of heroin. Given that participants typically use between one and 2 bags of heroin per occasion, the effects of higher doses of heroin during the early weeks of the study would have provided useful information. However, because the present experiment was a late phase 1 study, and we did not have information regarding the duration of antagonism of opioid effects, we chose not to test higher heroin doses because of safety concerns. In addition, because of uncertainty about the effects of 25 mg heroin in non-dependent individuals, we chose to administer active heroin doses in ascending order in the present study. Therefore, order effects could have influenced responses on our outcome measures. Future studies will evaluate higher doses of heroin in the early weeks following administration of depot naltrexone, and heroin doses will be administered in non-systematic order.

One interesting finding in the present study was a dramatic difference in ratings of "I Want Heroin" in the low-dose group, relative to the high-dose group. Participants in the low-dose group had consistently lower scores for this item across study weeks and heroin doses. The differences in wanting heroin were perhaps related to the possibility that participants in the high-dose group were experiencing greater withdrawal. Consistent with this notion is the fact that throughout the study, pupil diameter was larger in the high-dose group, compared to the low-dose group. However, one argument against this possibility is that subjective ratings of withdrawal were negligible, and did not differ between groups from study weeks 2–6. In clinical settings, it is generally accepted that craving for heroin is reduced during the early weeks after treatment is initiated, perhaps due to a perception that heroin is unavailable under antagonist maintenance (e.g. Mirin et al. 1976; Hollister et al. 1977; Sideroff et al. 1978; Judson et al. 1981). However, it is interesting to note that in one clinical study comparing 60 and 120 mg thrice-weekly administration of oral naltrexone, craving for heroin increased in both groups during weeks in which heroin was used, but the increase in craving was significantly greater in the 120 mg group (Judson et al. 1981). As in the present study, Judson et al. (1981) had no clear explanation for why craving was greater in the group maintained on the higher dose of naltrexone.

Future studies are needed to evaluate more systematically the effects of depot naltrexone on craving for heroin. A possible theory may relate to the effects of the higher dose of naltrexone on endogenous ligands, such as endorphin.

Another issue that warrants attention is the effect of depot naltrexone on liver enzymes. The package insert for oral naltrexone warns of an increased risk of hepatocellular injury. Given the high rate of hepatitis in intravenous drug abusers, combined with the possibility that naltrexone itself may produce hepatocellular injury, we carefully monitored liver enzymes throughout the study, and only admitted participants whose liver enzymes were within the laboratory normal range at baseline. Under these conditions, depot naltrexone did not produce clinically significant increases in liver enzyme levels. These results were consistent with several studies demonstrating a lack of effect of naltrexone on liver functioning, even after daily administration of high doses of naltrexone (100–350 mg; Brahen et al. 1988; Sax et al. 1994; Marrazzi et al. 1997). In fact, liver enzyme levels actually decreased in alcoholics who were treated with 50 mg per day of oral naltrexone, presumably due to the fact that they were drinking less alcohol (Volpicelli et al. 1997). Similarly, a previous study of depot naltrexone in the treatment of alcoholics showed that liver enzyme values decreased (Kranzler et al. 1998). Therefore, it appears that the formulation of naltrexone used in the present study has minimal effects on liver functioning, which is not entirely unexpected, given the fact that plasma naltrexone levels in the present study were equivalent to a relatively low dose of oral naltrexone.

There were few adverse events, other than an initial discomfort associated with the actual injections of depot naltrexone and mild soreness at the injection site for 2–3 days following the injections. Kranzler et al. (1998), who tested a single injection of the same formulation of depot naltrexone used in the present study, also noted that participants reported pain upon administration of depot naltrexone. In addition, these investigators reported that in 13 of 15 participants, an area of induration occurred at the injection site, which resolved over a period of 2.8 weeks (Kranzler et al. 1988). Induration was not found in the present study. Other negative side-effects typically reported after naltrexone administration are predominantly related to mood or gastrointestinal complaints (e.g. Hollister et al. 1981; Greenstein et al. 1984; Crowley et al. 1985; Shufman et al. 1994; Oncken et al. 2001), but these effects were not observed in the present study.

In addition to the discomfort associated with the injection itself, it is possible that depot naltrexone itself exacerbated withdrawal discomfort. The elevated SOWS scores in the high-dose group shown in Fig. 3 seem to provide support for this notion. However, this possibility is unlikely for a number of reasons. First, on the day prior to administration of 384 mg depot naltrexone, mean SOWS scores were 18.7 (± 9.0), and on the day that depot naltrexone was administered, mean scores were only

slightly higher at 20.8 (± 4.9). Therefore, depot naltrexone did not appear to exacerbate withdrawal in the high-dose group. SOWS scores in the low-dose group were also not different immediately before and after administration of depot naltrexone. Second, up to 50 mg oral naltrexone was administered for several consecutive days prior to administration of depot naltrexone. Given that 384 mg depot naltrexone produced blood levels of naltrexone comparable to approximately 12.5 mg oral naltrexone, it is unlikely that depot naltrexone would have exacerbated withdrawal. And finally, during a debriefing session at the end of the study, we specifically asked each participant whether he felt withdrawal symptoms after receiving the injections of depot naltrexone, and none claimed to experience any symptoms. Therefore, it is likely that the elevated SOWS scores in the high-dose group during the first week after administration of depot naltrexone reflects lingering baseline differences in withdrawal, rather than any direct effects of depot naltrexone. In a treatment setting where oral naltrexone may not be given prior to depot naltrexone administration, exacerbation of withdrawal could be avoided by lengthening the duration of the detoxification, and/or making ancillary medications, such as clonidine and benzodiazepines, available following administration of depot naltrexone.

In sum, the data presented in the current study demonstrate that this formulation of naltrexone produced a long-lasting antagonism of the effects of intravenous heroin, with minimal side-effects. Given that the primary difficulty associated with naltrexone maintenance in opioid abusers is medication compliance (Kosten and Kleber 1984; Fram et al. 1989; Preston et al. 1999), a formulation of naltrexone that requires only once-a-month administration has important and exciting treatment implications. Future studies in our laboratory will evaluate the clinical utility of depot naltrexone in the treatment of heroin dependence.

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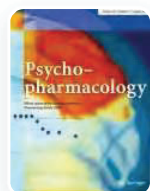
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Depot naltrexone: long-lasting antagonism of the effects of heroin in humans

Original Investigation Published: February 2002

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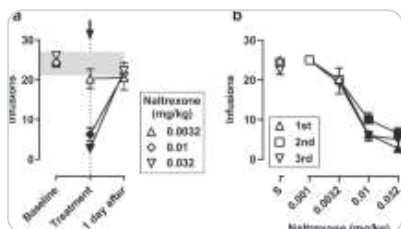
Abstract.

Rationale: Naltrexone, an opioid antagonist, is currently approved as a treatment for heroin dependence. However, naltrexone is generally not well accepted by patients, and medication non-compliance is a difficult obstacle to treatment. A sustained-release form of naltrexone may improve compliance. **Objective:** The present study was designed to evaluate the time course, safety, and effectiveness of a depot formulation of naltrexone (Depotrex[®]). **Methods:**

Twelve heroin-dependent individuals participated in an 8-week inpatient study. After a 1-week detoxification period, six participants received 192 mg naltrexone base and six participants received 384 mg naltrexone base. For safety, the low dose of depot naltrexone was tested before the high dose. The effects of heroin (0, 6.25, 12.5, 18.75, 25 mg, IV) were evaluated for the next 6 weeks. One dose of heroin was tested per day on Mondays through Fridays, and the entire dose range was tested each week. Active heroin doses were administered in ascending order during the week, while placebo could be administered on any day. Subjective, performance, and physiological effects were measured both before and after heroin administration. The hypotheses were that depot naltrexone would antagonize the effects of heroin, and that the high dose of depot naltrexone would produce a more effective and longer-lasting antagonism than the low dose. *Results:* The low and high doses of depot naltrexone antagonized heroin-induced subjective ratings for 3 and 5 weeks, respectively. Plasma levels of naltrexone remained above 1 ng/ml for approximately 3 and 4 weeks after administration of 192 mg and 384 mg naltrexone. Other than the initial discomfort associated with the injection of depot naltrexone, there were no untoward side-effects. *Conclusions:* These results suggest that this depot formulation of naltrexone provides a safe, effective, long-lasting antagonism of the effects of heroin.

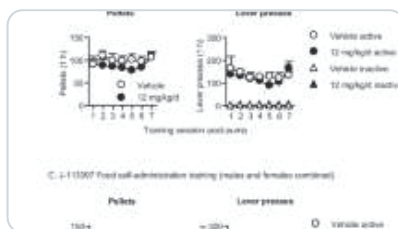
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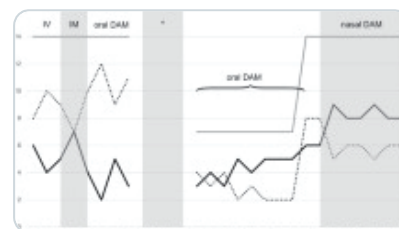
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Appendix COMER02

Sandra D. Comer · Eric D. Collins
Herbert D. Kleber · Elie S. Nuwayser
James H. Kerrigan · Marian W. Fischman

Depot naltrexone: long-lasting antagonism of the effects of heroin in humans

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Abstract *Rationale:* Naltrexone, an opioid antagonist, is currently approved as a treatment for heroin dependence. However, naltrexone is generally not well accepted by patients, and medication non-compliance is a difficult obstacle to treatment. A sustained-release form of naltrexone may improve compliance. *Objective:* The present study was designed to evaluate the time course, safety, and effectiveness of a depot formulation of naltrexone (Depotrex®). *Methods:* Twelve heroin-dependent individuals participated in an 8-week inpatient study. After a 1-week detoxification period, six participants received 192 mg naltrexone base and six participants received 384 mg naltrexone base. For safety, the low dose of depot naltrexone was tested before the high dose. The effects of heroin (0, 6.25, 12.5, 18.75, 25 mg, IV) were evaluated for the next 6 weeks. One dose of heroin was tested per day on Mondays through Fridays, and the entire dose range was tested each week. Active heroin doses were administered in ascending order during the week, while placebo could be administered on any day. Subjective, performance, and physiological effects were measured both before and after heroin administration. The hypotheses were that depot naltrexone would antagonize the effects of heroin, and that the high dose of depot naltrexone would produce a more effective and longer-lasting antagonism than the low dose. *Results:* The low and high doses of depot naltrexone antagonized heroin-induced subjective ratings for 3 and 5 weeks, respectively. Plasma levels of naltrexone remained above 1 ng/ml for approximately 3 and 4 weeks after administration of 192 mg and 384 mg naltrexone. Other than the initial discomfort associated with the injection of depot

naltrexone, there were no untoward side-effects. *Conclusions:* These results suggest that this depot formulation of naltrexone provides a safe, effective, long-lasting antagonism of the effects of heroin.

Keywords Heroin · Human · Naltrexone · Opioid · Subjective effect · Sustained-release · Depotrex

Introduction

Naltrexone, an orally effective opioid antagonist, was approved in 1984 by the Food and Drug Administration as a maintenance medication for the treatment of heroin dependence. Naltrexone potently antagonizes the effects of opioid agonists, while producing no agonist effects of its own (Jaffe and Martin 1990). Tolerance does not develop to naltrexone's antagonist effects and the drug has few side effects, even after chronic administration of over 1 year (Kleber et al. 1985). Because of its ability to antagonize the effects of mu opioid agonists, its long duration of action, and its favorable pharmacokinetic and metabolic characteristics (Martin et al. 1966, 1973), naltrexone initially held great promise as a treatment for opioid dependence. The early rationale for using a pure antagonist was that once the individual was maintained on naltrexone, subsequent attempts to self-administer the illicit opioid would not produce euphoria (Wikler 1965; Martin et al. 1966) and the user would eventually discontinue opioid use altogether.

Although the use of naltrexone as a maintenance therapy for opioid abuse can be effective (Martin et al. 1973; O'Brien et al. 1975; Judson et al. 1981), it has been used most successfully with only a select subpopulation of highly motivated individuals. Because of the problems with medication non-compliance, naltrexone therapy has not lived up to its initial promise. This may be in part because opioid users are accustomed to self-administering potent reinforcers, and, by contrast, the complete absence of opioid-induced reinforcing effects may be unacceptable. Another factor that may contribute to noncom-

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Table 1 Participant demographics. Numbers in parentheses represent ± 1 SEM

	192 mg naltrexone	384 mg naltrexone
Age (average; years)	33.8 (2.5)	29.2 (3.2)
Years of heroin use (average)	10.7 (2.5)	9.1 (3.5)
Amount spent for heroin (average; \$/day)	\$39 (4)	\$55 (12)
Tobacco cigarette use (range; no. per day)	8–20	10–20
Cocaine use (range; occasions/week)	0–1	0–3
Amphetamine use (range; occasions/week)	0–1	0
Marijuana use (range; occasions/week)	0–1	0–3
Alcohol use (range; occasions/week)	0–1	0–3
Sedative use (range; occasions/week)	0–1	0–1

pliance is that, unlike methadone, discontinuation of naltrexone maintenance has no adverse consequences (e.g. withdrawal effects). Furthermore, naltrexone itself may induce adverse neuropsychiatric and gastrointestinal effects, such as dysphoria, nausea, and abdominal pain (Hollister et al. 1981; Crowley et al. 1985; Oncken et al. 2001).

Sustained-release forms of naltrexone could increase compliance and ultimately improve treatment effectiveness (Martin and Sandquist 1974; Abrahams and Ronel 1975; Chiang et al. 1985a, 1985b). Chiang et al. (1985a, 1985b), for example, administered biodegradable beads containing a dose of 63 mg naltrexone to normal, healthy volunteers. Following an initial burst of release, this formulation yielded relatively constant plasma levels of naltrexone (0.3–0.5 ng/ml) for up to 1 month. However, when these investigators administered challenge doses of morphine (15 mg IM), the results were variable. In some participants, morphine was completely ineffective, while in others, morphine-like effects were observed. In addition, three of the five participants who completed the study developed tissue inflammation near the site of bead implantation (Chiang et al. 1985b). Although the adverse tissue reaction and the variable antagonist effectiveness of the naltrexone beads limited its clinical utility, the rationale behind the development of a sustained-release form of naltrexone was sound.

A new depot formulation of naltrexone (Depotrex®) has been developed that provides a stable, long-lasting elevation in plasma naltrexone levels with either no or minimal side-effects (Heishman et al. 1994; Alim et al. 1995; Kranzler et al. 1998). In an early tolerability study, Alim and colleagues (1995) reported blockade of the physiological and subjective effects of 10 mg intravenous (IV) morphine in cocaine-dependent participants who received 206 mg depot naltrexone; side-effects associated with naltrexone were minimal in these participants. Kranzler and colleagues (1998) further showed that 206 mg depot naltrexone significantly reduced the percentage of heavy drinking days in alcoholics. Adverse effects reported after depot naltrexone were comparable to those reported after oral naltrexone administration. Although this formulation of depot naltrexone appears to be safe and effective in treating alcohol dependence, it has not yet been tested with heroin. The purpose of the current study was 1) to determine whether the new formulation of depot naltrexone will antagonize the effects

of heroin at doses comparable to those used on the streets today, and 2) to assess the duration of antagonist effect of 192 mg and 384 mg depot naltrexone. The hypothesis was that depot naltrexone would dose-dependently antagonize the effects of heroin.

Materials and methods

Participants

Fifteen heroin-dependent men, who were not seeking treatment for their drug use, began the 8-week protocol. Three participants left the study prior to depot naltrexone administration: one was discharged for aggressive behavior toward the staff, and two left for personal reasons. Twelve participants (eight non-Hispanic Caucasian, three Hispanic, and one African American) completed the study: six received 192 mg depot naltrexone, and six received 384 mg depot naltrexone (Table 1). The low dose of depot naltrexone was tested in the first six participants. The groups did not differ in age, years of heroin use, and amount of money spent on heroin per day. All participants had experience using heroin IV. One participant in the low-dose group and two in the high-dose group preferred to use heroin intranasally; all other participants preferred to use heroin IV. All participants were dependent on heroin at the start of the study, as verified by a naloxone challenge test (Wang 1974).

After an initial telephone interview, eligible participants completed detailed questionnaires on drug use, general health and medical history, and a medical and psychological evaluation in the laboratory. An electrocardiogram and Mantoux test or chest X-ray were also performed. Routine laboratory analyses included a blood chemistry panel, thyroid function test, syphilis and hepatitis (A, B, and C) screening, and urinalysis. Urine drug toxicologies (opioids, cocaine, benzodiazepines, cannabinoids, and amphetamines) were also performed using a radiative energy attenuation and fluorescence polarization immunoassay system (AD_x System; Abbott Laboratories, Abbott Park, Ill., USA). Participants were told that they would be detoxified from heroin during the first week of the study, that they would receive one of two doses of a depot formulation of naltrexone, and that a range of IV heroin doses would be tested each week for the 6 weeks following depot naltrexone administration.

Participants were excluded from the study if they were seeking drug treatment, dependent on alcohol or illicit drugs other than opioids, or had a major Axis I psychiatric diagnosis other than opioid dependence. Those who had recent histories of violence or who were on parole/probation were excluded from the study. Participants were required to be physically healthy, and fully able to perform all study procedures. Although both men and women were screened for the study, none of the women met the eligibility requirements. Prior to admission, participants completed a training session, during which the study procedures were explained to them in detail. Volunteers were paid \$25 per inpatient day and an additional \$25 per day bonus if they completed the study. Participants signed consent forms describing the aims of the study, and

the potential risks and benefits of participation. Free HIV testing and education were offered, and during the last week of the study, participants were offered referrals for treatment. This study was approved by the Institutional Review Board of the New York State Psychiatric Institute (NYSPI).

Apparatus

During experimental sessions, participants were seated in a room equipped with Macintosh computers. All computer activities, vital signs and behaviors were continuously monitored by the experimenters in an adjacent control room via a continuous on-line computer network, video cameras, and vital signs monitors (cardiovascular function was measured using a Sentry II Vital Signs Monitor, NBS Medical, Costa Mesa, Calif., USA; arterial oxygen saturation was measured using a pulse oximeter Model 400, Palco Laboratories, Santa Cruz, Calif., USA). Communication between the staff and participants was kept to a minimum during experimental sessions.

Detoxification procedures

Participants were admitted into the hospital, and detoxified during the first week after admission. Buprenorphine (8 mg sublingual tablet; National Institute on Drug Abuse, Rockville, Md., USA) was administered on the first 1–2 days after admission. Two days after the last buprenorphine dose, oral naltrexone (DuPont Pharma, Wilmington, Del., USA) was administered for 3 consecutive days (25, 50, and 50 mg per day) to ensure that participants were willing and able to tolerate its effects. Clonidine HCl (0.2 mg PO, every 6 h; Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Conn., USA), ketorolac tromethamine (30 mg IM, every 6 h; Roche Laboratories, Nutley, N.J., USA), prochlorperazine (10 mg PO or IM, every 8 h; SmithKline Beecham Consumer Healthcare, Pittsburgh, Penn., USA) and clonazepam (2 mg PO, every 8 h; Roche Laboratories) were available, as needed, during the detoxification week. Thereafter, trazodone (50–100 mg PO, at bedtime; Warner Chilcott, Morris Plains, N.J., USA) was available if participants reported having trouble sleeping. Depot naltrexone was administered on a Monday morning, 2 days after the last oral naltrexone dose.

General procedures

The effects of IV heroin (placebo, 6.25, 12.5, 18.75, and 25 mg) were evaluated each week for 6 weeks following depot naltrexone administration. The entire dose range was tested each week, and one dose of heroin was tested each day on weekdays. For safety, active heroin doses were administered in ascending order within each week, with the exception that the day of placebo injection was varied across weeks. On the day that depot naltrexone was administered, placebo was tested during the experimental session.

Experimental sessions

During all sessions, participants completed computerized tasks and subjective-effects questionnaires. Heart rate and blood pressure were measured every 2 min, and blood oxygen saturation was monitored continuously with a pulse oximeter and recorded every minute during experimental sessions. Participants received breakfast between 0800 and 0900 and lunch between 1230 and 1330 hours. Experimental sessions occurred between 0930 and 1130 hours. Participants were not allowed to smoke tobacco cigarettes during experimental sessions.

Physiologic, subjective and performance effects were measured both before and after drug administration (see descriptions below). Heroin or placebo was administered only if vital signs were within safe limits ($\text{SpO}_2 > 93\%$). A photograph was taken of the right pupil before and 4, 10, 20, 40 and 60 min after drug ad-

ministration. The subjective-effects battery (see description below) was administered before and 4, 40 and 90 min after drug administration. The performance battery (see description below) was administered before and 10 and 60 min after drug administration. The Subjective Opioid Withdrawal Scale was administered before drug administration. The Drug Effects Questionnaire was administered 90 min after drug administration.

Subjective measures

Four questionnaires were used to assess subjective effects throughout the experimental sessions. The first questionnaire was a 26-item visual analog scale (VAS) designed to assess subjective and physiological effects (modified from Foltin and Fischman 1995). The first 18 lines were labeled with adjectives describing mood states (e.g., "I feel..." "high") and four additional lines, labeled with questions about the dose just received (i.e. "I liked the dose," "For this dose, I would pay"). Participants also indicated, by making a mark along a 100 mm line, how much they "wanted" each of the following drugs: heroin, cocaine, alcohol, and tobacco. Participants rated each item on the VAS from "Not at all" (0 mm) to "Extremely" (100 mm), except for the "For this dose, I would pay" question, which ranged between \$0 (0 mm) to \$20 (100 mm). The second questionnaire was a 13-item opioid symptom checklist consisting of true/false questions designed to measure opioid effects (e.g. "My skin is itchy," etc.; Fraser et al. 1961; Foltin and Fischman 1992). The VAS and opioid symptom checklist together constituted the subjective-effects battery. The third questionnaire was the 16-item Subjective Opioid Withdrawal Scale (SOWS; Handelsman et al. 1987). Participants rated each item on a scale from 0 to 4, with 0 being "Not at all" and 4 being "Extremely" (e.g. "I have gooseflesh," etc.). The fourth questionnaire was a 6-item Drug Effects Questionnaire (DEQ; Evans et al. 1995). Participants described drug effects by selecting among a series of possible answers ranging from 0 ("No effects at all") to 4 ("Very strong (good, bad, etc.) effects"). Ratings of drug liking ranged between -4 ("Dislike very much") to 4 ("Like very much").

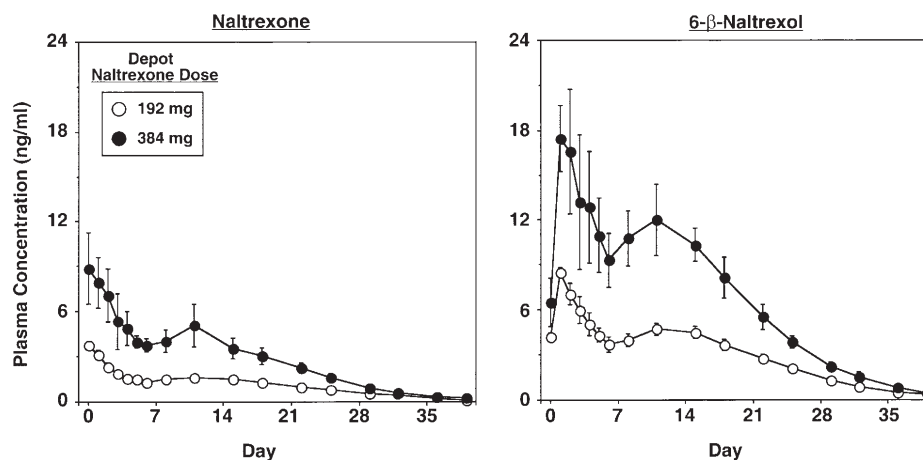
Task battery

The task battery consisted of four tasks: the first task was a 3-min digit-symbol substitution task, during which participants were required to emulate a series of patterns on a keypad (McLeod et al. 1982). The second task was a 10-min divided attention task, which consisted of concurrent pursuit-tracking and vigilance tasks (Miller et al. 1988). The third task was a 10-min rapid information processing task, during which a series of digits was displayed rapidly on the computer screen (100 digits/min), and participants were instructed to press a key as quickly as possible after three consecutive odd or even digits (Wesnes and Warburton 1983). The fourth task was a 3-min repeated acquisition of response sequences task, during which four buttons were illuminated, and participants were instructed to learn a ten-response sequence of button presses (Kelly et al. 1993).

Physiological measures

A blood pressure cuff was attached to the non-dominant arm, which recorded automatically every 2 min. Participants were also connected to a pulse oximeter via a soft sensor on a finger of the dominant hand, which monitored arterial blood oxygen saturation ($\%\text{SpO}_2$). For safety, supplemental oxygen (2 l/min) was provided via a nasal cannula during all experimental sessions. A specially modified Polaroid camera with a close-up lens ($\times 2$ magnification) was used to take pupil photographs. All photographs were taken under ambient lighting conditions. Horizontal and vertical measurements of pupil diameter were made using calipers, and then these two measurements were averaged and divided by 2 to correct for the $\times 2$ magnification.

Fig. 1 Mean plasma levels of naltrexone (*left panel*) and 6- β -naltrexol (*right panel*) as a function of depot naltrexone dose and days after administration of depot naltrexone. Data points represent the mean across 6 participants per group. Error bars represent ± 1 SEM



Blood was drawn 2 h, 1, 2, 3, 4, 5, 6, 8, 11, 15, 18, 22, 25, 29, 32, 36, and 39 days after administration of depot naltrexone, and immediately centrifuged at 3000 rpm for 15 min. Plasma was drawn off and stored at -20°C until it was shipped by overnight mail on dry ice for analyses of naltrexone and 6- β -naltrexol (Center for Human Toxicology, University of Utah, Salt Lake City, Utah, USA). Analyses were performed by solid phase extraction and negative ion chemical ionization gas chromatography/mass spectrometry, as described by Huang and colleagues (1997). The lower limit of detectability for both analytes was 0.1 ng/ml.

Blood was also drawn prior to, and at weekly intervals after administration of depot naltrexone for analyses of liver enzymes (AST, ALT, GGT).

Drugs

Depot naltrexone (Depotrex[®]) was manufactured by Biotek Inc. (Woburn, Mass., USA) and provided by the National Institute on Drug Abuse. Depotrex is a registered trademark of Biotek, Inc. Naltrexone microcapsules and placebo microspheres were packaged in sterile single-dose vials. After reconstituting in suspending medium, 2.4 ml of the suspension was injected. The active formulation contained drug equivalent to 192 mg naltrexone base. The placebo formulation contained the equivalent weight in polymer microspheres. Injections were administered subcutaneously into the buttocks (one injection per buttock), using an 18 gauge needle. For the low dose, participants received one placebo and one naltrexone injection (192 mg naltrexone base), and for the high dose, participants received two naltrexone injections (394 mg naltrexone base). For safety, the low dose of Depotrex was tested in the first six participants, and the high dose of Depotrex was tested in the next six participants.

Heroin HCl was provided by the National Institutes on Drug Abuse and prepared by the Columbia-Presbyterian Medical Center research pharmacy. A 25 mg/ml heroin concentration was prepared in a 5% dextrose solution to enhance stability. Dose calculations were based on the hydrochloride salt form. Heroin was stored in a freezer and used within 3 months of preparation. The stock solution was diluted in 5% dextrose to produce each dose. Placebo (5% dextrose solution) or heroin (6.25, 12.5, 18.75, and 25 mg) was administered intravenously over a 30-s period in a total volume of 2 ml. Heroin doses were administered in a double-blind fashion. Physiological saline solution was infused continuously during experimental sessions, except during drug administration. Between 1 and 2 ml heparinized saline (10 IU/ml) was flushed into the catheter four to eight times each day. All venous catheters were maintained as heparin locks and were removed within 72 h of insertion.

Supplemental medications available to all participants for the duration of the study included: Mylanta, acetaminophen, ibuprofen, Colace, Milk of Magnesia and multi-vitamins with iron.

Morning urine samples were collected daily and one random sample per week was screened for the presence of other illicit substances. No illicit substances were found in the participants' urine samples.

Statistical analyses

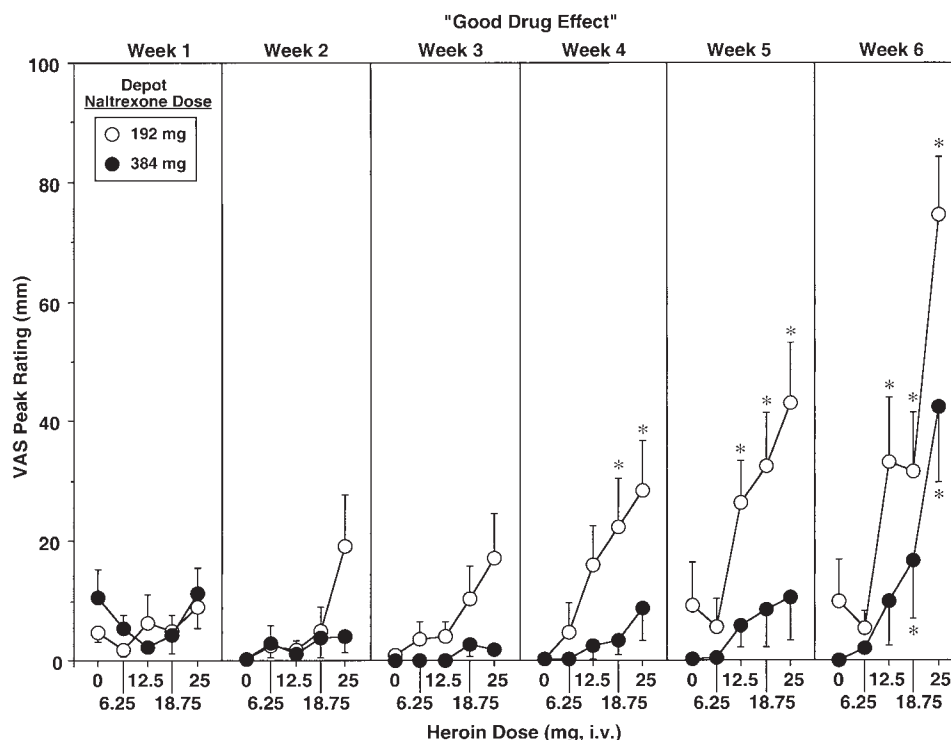
Repeated-measures analyses of variance (ANOVA) with planned comparisons were used to address the following questions: 1) What was the duration of antagonism of heroin's effects? 2) Did the low and high doses of depot naltrexone differ in ability to antagonize the effects of heroin? In order to address the first question, the data for each group were analyzed separately as a function of week (1–6) and heroin dose (0, 6.25, 12.5, 18.75, 25 mg). Twenty-five planned comparisons were made: each week (2–6) was compared to week 1 for each dose (e.g. placebo-week 2 versus placebo-week 1, placebo-week 3 versus placebo-week 1, placebo-week 4 versus placebo-week 1, etc.) because it was likely that virtually complete antagonism would occur during week 1. In order to address the second question, an overall analysis was performed with one between-group factor (group) and two within-group factors (week, heroin dose): the main effect of group, and the week $\times$ group and dose $\times$ group effects were evaluated. Interaction effects were examined using post-hoc comparisons. Peak subjective ratings, peak performance effects, trough pupil diameter, liver enzyme levels, average arterial oxygen saturation, and plasma levels of naltrexone and 6- β -naltrexol were analyzed. Liver enzymes (AST, ALT, GGT) were also analyzed: each week post-depot naltrexone was compared to a pre-depot naltrexone baseline. Due to an excessive number of missing data points, the cardiovascular data were not analyzed. To control for type I errors, a modified Bonferroni test was used in that only those comparisons with $P < 0.01$ were considered statistically significant.

Results

Plasma drug levels

Figure 1 shows mean plasma levels of naltrexone (left panel) and 6- β -naltrexol (right panel) for each group as a function of time since the depot naltrexone injection. Two hours after administration of 192 mg and 384 mg depot naltrexone, plasma levels of naltrexone were 3.8 (± 0.2) and 8.9 (± 1.4) ng/ml. Plasma levels of 6- β -naltrexol were 8.5 (± 0.3) and 17.4 (± 1.3) ng/ml, respectively, 24 h after administration of 192 mg and 384 mg depot naltrexone. Across individual participants, plasma levels

Fig. 2 Mean peak VAS ratings of "Good Drug Effect" after administration of heroin (0–25 mg) as a function of depot naltrexone dose and study week (week 1: *left panel*; week 6: *right panel*). Maximum rating=100 mm. Data points represent mean peak ratings ($n=6$ per group). Error bars represent ± 1 SEM. * Indicates significant differences from week 1



of naltrexone ranged between 3.1 and 4.5 ng/ml after administration of 192 mg depot naltrexone, and 5.6 and 14.2 ng/ml after administration of 384 mg depot naltrexone. After administration of 192 mg and 384 mg of depot naltrexone, plasma levels of naltrexone were less than 1 ng/ml on day 22 and 29, respectively. The group and group $\times$ day effects for naltrexone [group: $F(1,10)=48.5$, $P<0.0001$; group $\times$ day: $F(1,10)=8.6$, $P<0.0001$] and 6- β -naltrexol [group: $F(1,10)=33.8$, $P<0.0002$; group $\times$ day: $F(1,10)=8.3$, $P<0.0001$] were significant.

Subjective effects

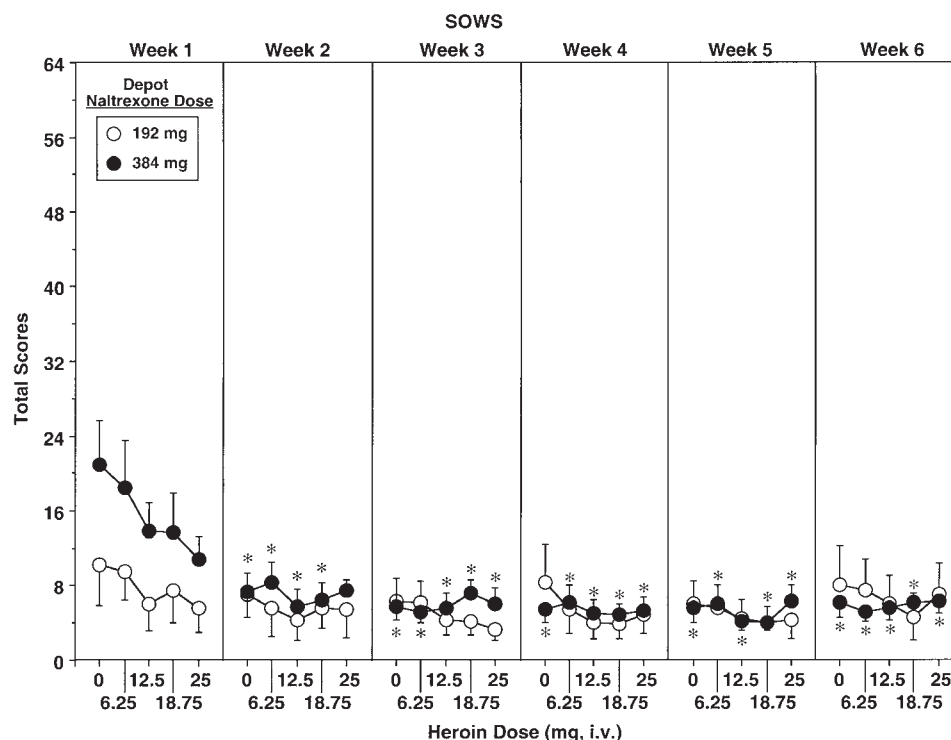
Figure 2 shows mean peak visual analog scale ratings of "Good Drug Effect" for each group as a function of heroin dose and week. After low-dose depot naltrexone, ratings of "Good Drug Effect" significantly increased by week 4, relative to week 1, after administration of 18.75 mg [$F(1,100)=6.4$, $P<0.01$] and 25 mg heroin [$F(1,100)=7.9$, $P<0.006$]; ratings of "Good Drug Effect" significantly increased by week 5 after administration of 12.5 mg heroin [$F(1,100)=8.4$, $P<0.004$]. In the high-dose group, ratings of "Good Drug Effect" did not significantly increase until week 6, after 18.75 mg [$F(1,100)=7.5$, $P<0.007$] and 25 mg heroin [$F(1,100)=47.3$, $P<0.0001$]. Both the week $\times$ group [$F(5,50)=4.8$, $P<0.001$] and dose $\times$ group [$F(4,40)=4.4$, $P<0.005$] effects were significant for ratings of "Good Drug Effect." Several other VAS ratings showed a similar pattern including ratings of "High," "Liking," drug "Potency," drug "Quality," and how much they would be willing to pay for the dose (data not shown). The dose $\times$ group

effect was significant [$F(4,40)=4.2$, $P<0.006$], and the week $\times$ group effect approached statistical significance [$F(5,50)=2.9$, $P<0.02$] for ratings of "High." Although ratings tended to be higher in the low-dose group for VAS ratings of "Liking," drug "Potency," and drug "Quality," the week $\times$ group and dose $\times$ group effects were not statistically significant for these items.

VAS ratings of "I feel..." "Gooseflesh," "Depressed," "Muscle Pain," "Anxious," and "Restless" were elevated in both groups during the first week after receiving depot naltrexone, and were higher in the high-dose group (data not shown). The week $\times$ group effect was statistically significant for ratings of "Gooseflesh" [$F(5,50)=3.4$, $P<0.01$] and "Depressed" [$F(5,50)=3.5$, $P<0.009$], while the week $\times$ group effect for ratings of "Muscle Pain" ($P<0.03$), "Anxious" ($P<0.04$), and "Restless" ($P<0.04$) approached statistical significance. Ratings of "I Want Heroin," which did not vary across study weeks or heroin doses, were significantly elevated in the high-dose group [main effect of group: $F(1,10)=26.3$, $P<0.0004$]. Ratings of "I Want Heroin" ranged between 26 and 37 in the low-dose group, and 86 and 95 in the high-dose group.

The pattern of results obtained from the opioid symptom checklist and DEQ (data not shown) were similar to the VAS ratings of "Good Drug Effect" (Fig. 2) in that total scores on the opioid symptom checklist and DEQ ratings of drug "Liking," "Good Drug Effect," strength of drug effect, and desire to take the drug again increased as a function of heroin dose and across study weeks. The week $\times$ group effect was statistically significant for the opioid symptom checklist [$F(5,50)=3.2$, $P<0.01$]. Although ratings tended to be higher in the

Fig. 3 Mean total scores on the Subjective Opioid Withdrawal Scale (SOWS) after administration of heroin as a function of depot naltrexone dose and study week. Maximum score=64. All other details are as in Fig. 2



low-dose group compared to the high-dose group, the week $\times$ group and dose $\times$ group effects were not statistically significant for any of the items on the DEQ.

Subjective ratings of opioid withdrawal, as measured by total scores on the SOWS, did not significantly differ between groups during detoxification, prior to administration of depot naltrexone. SOWS scores peaked on day 4 after admission: total SOWS scores on day 4 of withdrawal were 22.5 ($\pm$ 11.2) and 26.3 ($\pm$ 7.3), out of a maximum possible score of 64, after administration of 192 and 384 mg depot naltrexone, respectively. On the day prior to administration of depot naltrexone, SOWS scores were 11.0 ($\pm$ 8.2) and 18.7 ($\pm$ 9.0) in the low- and high-dose groups, respectively. Figure 3 shows total SOWS scores after administration of depot naltrexone for each group as a function of heroin dose and week. Total SOWS scores were significantly elevated during the first week in the high-dose group, but not in the low-dose group. By the second week after administration of depot naltrexone, SOWS scores did not differ between groups. The week $\times$ group interaction for total SOWS scores approached statistical significance [$F(5,50)=2.5$, $P<0.04$].

Performance tasks

Heroin minimally affected task performance, with the exception that performance of the divided attention task was significantly impaired: in the low-dose group, the latency to identify a target significantly increased by 1.7 s during week 5, relative to week 1, after administration of 25 mg heroin [$F(1,100)=8.3$, $P<0.005$]. In the high-dose group, the latency to identify a target signifi-

cantly increased by 1.3 s during week 6, relative to week 1, after administration of 25 mg heroin [$F(1,100)=30.9$, $P<0.0001$]. Latency to identify a target did not significantly change across weeks after administration of placebo in either group. The week $\times$ group and dose $\times$ group effects were not statistically significant for latency to identify a target during the divided attention task.

Physiological effects

Figure 4 shows the effects of heroin on pupil diameter for each group as a function of heroin dose and week. During week 1, pupil diameter was large in both groups, consistent with the possibility that both groups were in mild withdrawal. After placebo administration during week 1, pupil diameter was 5.3 ($\pm$ 0.3) and 5.6 ($\pm$ 0.6) mm in the low- and high-dose groups, respectively. Pupil diameter was relatively stable under the placebo condition in both groups from weeks 2–6 (Fig. 4), although pupil diameter consistently remained larger in the high-dose group throughout the study. After administration of active doses of heroin, pupil diameter progressively decreased across study weeks in both groups. The week $\times$ group and dose $\times$ group effects were not significant for pupil diameter.

The average arterial oxygen saturation significantly decreased by 0.9% in both groups from week 1 to week 6, after administration of 25 mg heroin [low-dose group: $F(1,100)=17.2$, $P<0.0001$; high-dose group: $F(1,100)=7.8$, $P<0.006$]. However, these changes in oxygen saturation occurred in the presence of supplemental oxygen, and were not clinically significant.

Fig. 4 Mean trough pupil diameter after administration of heroin as a function of depot naltrexone dose and study week. All other details are as in Fig. 2

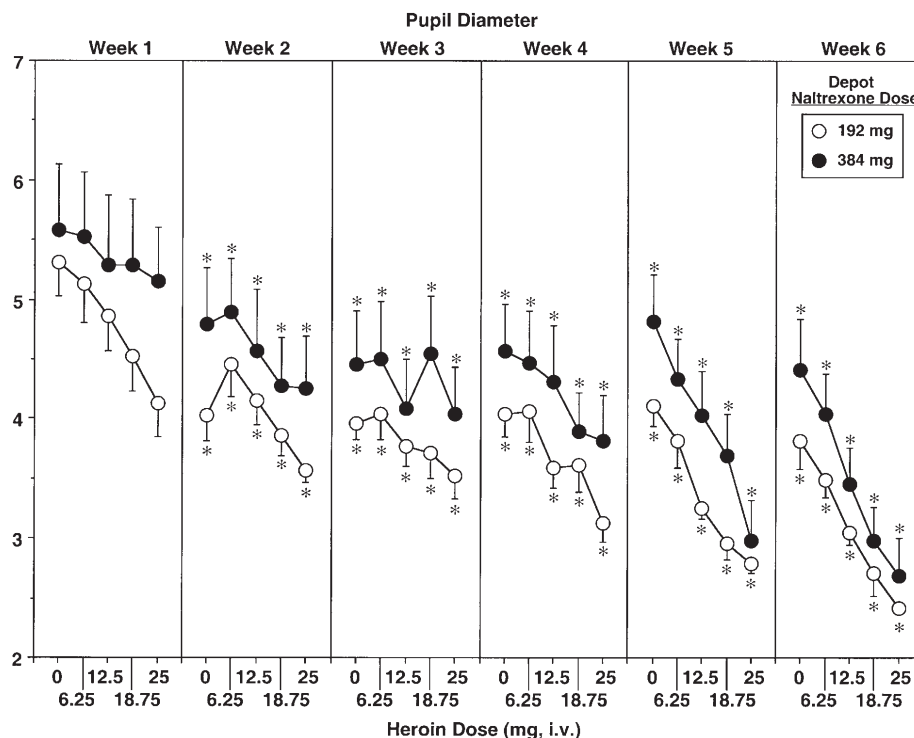


Table 2 ALT, AST, and GGT values (IU/l) at baseline and for 6 weeks following administration of 192 mg or 384 mg depot naltrexone. Numbers in parentheses represent ± 1 SEM. Asterisks represent significant differences from baseline ($P < 0.01$)

	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
192 mg							
ALT	29.2 (7.2)	54.7 (22.2)	63.3 (26.5)	65.3 (25.8)	75.2 (31.0)*	60.7 (21.4)	34.3 (6.3)
AST	19.7 (2.3)	27.8 (6.9)	31.2 (7.4)	26.8 (6.2)	34.7 (8.9)*	31.5 (7.8)	22.5 (3.1)
GGT	42.3 (17.5)	39.7 (14.6)	46.8 (14.6)	55.0 (18.4)*	62.3 (20.7)*	56.7 (18.0)*	45.7 (16.1)
384 mg							
ALT	24.3 (7.2)	132.3 (99.8)	51.8 (17.4)	45.5 (16.0)	50.0 (20.0)	53.3 (24.2)	49.0 (21.6)
AST	21.5 (3.7)	31.8 (5.9)	22.8 (4.8)	24.7 (5.5)	29.5 (6.5)	36.2 (11.8)	31.0 (6.8)
GGT	28.7 (9.7)	55.0 (24.0)	47.5 (16.4)	40.0 (11.7)	40.2 (12.1)	39.0 (11.3)	36.0 (11.3)

Liver enzyme (ALT, AST, GGT) values at baseline were within the normal range for all participants, with the exception of one individual in the low-dose group whose GGT value (128 IU/l) slightly exceeded the normal range of 5–80 IU/l. Three individuals in the low-dose group tested positive for hepatitis, and four individuals in the high-dose group tested positive for hepatitis. In the low-dose group, average GGT levels significantly increased during weeks 3, 4, and 5, relative to baseline [Tables 2; week 3: $F(1,30)=7.5$, $P<0.01$; week 4: $F(1,30)=18.6$, $P<0.0002$; week 5: $F(1,30)=9.6$, $P<0.004$]. Both ALT [$F(1,30)=7.5$, $P<0.01$] and AST [$F(1,30)=8.5$, $P<0.007$] values in the low-dose group significantly increased during week 4, relative to baseline. Although these liver enzyme values following administration of the low dose were statistically significant, it is important to note that they were not clinically significant. The increases in liver enzyme values in the low-dose group were predominantly due to one hepatitis-negative individual: his baseline

GGT value was 54 IU/l, which peaked at 226 IU/L during week 4, and returned to 54 IU/l by week 6. Liver enzyme levels did not significantly change across study weeks in the high-dose group. The non-significant, transient increase in ALT values during week 1 in the high-dose group was due to one individual who received several doses of ketorolac tromethamine during detoxification. His liver enzyme levels peaked at 630 IU/l during week 1, and returned to normal (32 IU/l) by week 3.

Side-effects

Eleven of 12 participants reported pain during administration of the depot injections. These individuals reported no discomfort while standing, and only mild discomfort at the injection sites while seated, during the first 48–72 h after the injections. There was no evidence of induration, erythema, or irritation. One participant who

inadvertently received one of the injections (placebo) intramuscularly reported pain on that side for the first 72–96 h after the injection.

Discussion

The depot formulation of naltrexone used in the current study provided a safe, effective, long-lasting antagonism of the effects of heroin. Across the time points measured, the highest naltrexone plasma levels attained after administration of 192 mg and 384 mg of depot naltrexone were $3.8 (\pm 0.2)$ and $8.9 (\pm 1.4)$ ng/ml, respectively. For comparison, Walsh et al. (1996) reported that daily administration of 50 mg oral naltrexone resulted in naltrexone plasma concentrations of approximately 30 ng/ml, while daily administration of 12.5 mg oral naltrexone resulted in naltrexone plasma concentrations of approximately 10 ng/ml (plasma samples were collected 30 min after administration of naltrexone). Therefore, the amount of drug found in plasma after depot naltrexone administration is lower than the amount found after a standard dose of naltrexone used clinically for treating heroin dependence (50 mg/day).

In the present study, antagonism of heroin's effects occurred, despite negligible plasma levels of naltrexone. An early study conducted by Vereby and colleagues (Vereby et al. 1976) showed that 100 mg oral naltrexone did not completely antagonize the effects of 25 mg IV heroin when plasma levels of naltrexone fell below approximately 2 ng/ml. In contrast, Navaratnam and colleagues (Navaratnam et al. 1994) showed that after discontinuation of day 1-day 3-day 5 dosing with 100–100–150 mg oral naltrexone, antagonism of the effects of 25 mg IV heroin continued to occur when plasma levels of naltrexone were negligible. Schuh and colleagues (Schuh et al. 1999) also demonstrated that during a "wash-out period" after discontinuation of daily administration of 100 mg oral naltrexone, antagonism of the effects of up to 4 mg IM hydromorphone continued to occur when plasma levels of naltrexone were negligible. The data presented in the current study were more consistent with those of Navaratnam et al. (1994) and Schuh et al. (1999) in that 384 mg depot naltrexone antagonized heroin-induced ratings of "I Feel High" and "I Feel a Good Drug Effect" for up to 5 weeks, even though plasma levels of naltrexone were quite low (0.3 ± 0.04 ng/ml). These data are not entirely surprising, given a previous study demonstrating that the percentage blockade of [^{11}C]carfentanil binding in the brain of normal healthy volunteers at 48, 72, 120, and 168 h after administration of 50 mg oral naltrexone was 91, 80, 46, and 30%, respectively (Lee et al. 1988). Results from the Lee et al. (1988) study suggest that orally delivered naltrexone continues to inhibit brain opioid receptors in the absence of measurable plasma levels of naltrexone. In the present experiment, it is also possible that 6- β -naltrexol, the active metabolite of naltrexone, contributed to the continued antagonism of heroin's effects, particularly

because plasma levels of this metabolite were consistently higher than naltrexone throughout the study.

In the present study, both doses of depot naltrexone initially antagonized the positive subjective effects of heroin, consistent with naltrexone's well-established effectiveness in blocking the subjective effects of opioid agonists (e.g. Altman et al. 1976; Mello et al. 1980; Preston and Bigelow 1993; Schuh et al. 1999). Although the present study clearly demonstrated a long-lasting antagonism of the subjective effects of up to 25 mg IV heroin, it did not address the question of what dose of heroin would effectively override the blockade during the first few weeks after administration of depot naltrexone. In previous studies in our laboratory, participants who were maintained on morphine reported that 25 mg heroin was roughly equivalent to one \$10 "street bag" of heroin. Given that participants typically use between one and 2 bags of heroin per occasion, the effects of higher doses of heroin during the early weeks of the study would have provided useful information. However, because the present experiment was a late phase 1 study, and we did not have information regarding the duration of antagonism of opioid effects, we chose not to test higher heroin doses because of safety concerns. In addition, because of uncertainty about the effects of 25 mg heroin in non-dependent individuals, we chose to administer active heroin doses in ascending order in the present study. Therefore, order effects could have influenced responses on our outcome measures. Future studies will evaluate higher doses of heroin in the early weeks following administration of depot naltrexone, and heroin doses will be administered in non-systematic order.

One interesting finding in the present study was a dramatic difference in ratings of "I Want Heroin" in the low-dose group, relative to the high-dose group. Participants in the low-dose group had consistently lower scores for this item across study weeks and heroin doses. The differences in wanting heroin were perhaps related to the possibility that participants in the high-dose group were experiencing greater withdrawal. Consistent with this notion is the fact that throughout the study, pupil diameter was larger in the high-dose group, compared to the low-dose group. However, one argument against this possibility is that subjective ratings of withdrawal were negligible, and did not differ between groups from study weeks 2–6. In clinical settings, it is generally accepted that craving for heroin is reduced during the early weeks after treatment is initiated, perhaps due to a perception that heroin is unavailable under antagonist maintenance (e.g. Mirin et al. 1976; Hollister et al. 1977; Sideroff et al. 1978; Judson et al. 1981). However, it is interesting to note that in one clinical study comparing 60 and 120 mg thrice-weekly administration of oral naltrexone, craving for heroin increased in both groups during weeks in which heroin was used, but the increase in craving was significantly greater in the 120 mg group (Judson et al. 1981). As in the present study, Judson et al. (1981) had no clear explanation for why craving was greater in the group maintained on the higher dose of naltrexone.

Future studies are needed to evaluate more systematically the effects of depot naltrexone on craving for heroin. A possible theory may relate to the effects of the higher dose of naltrexone on endogenous ligands, such as endorphin.

Another issue that warrants attention is the effect of depot naltrexone on liver enzymes. The package insert for oral naltrexone warns of an increased risk of hepatocellular injury. Given the high rate of hepatitis in intravenous drug abusers, combined with the possibility that naltrexone itself may produce hepatocellular injury, we carefully monitored liver enzymes throughout the study, and only admitted participants whose liver enzymes were within the laboratory normal range at baseline. Under these conditions, depot naltrexone did not produce clinically significant increases in liver enzyme levels. These results were consistent with several studies demonstrating a lack of effect of naltrexone on liver functioning, even after daily administration of high doses of naltrexone (100–350 mg; Brahen et al. 1988; Sax et al. 1994; Marrazzi et al. 1997). In fact, liver enzyme levels actually decreased in alcoholics who were treated with 50 mg per day of oral naltrexone, presumably due to the fact that they were drinking less alcohol (Volpicelli et al. 1997). Similarly, a previous study of depot naltrexone in the treatment of alcoholics showed that liver enzyme values decreased (Kranzler et al. 1998). Therefore, it appears that the formulation of naltrexone used in the present study has minimal effects on liver functioning, which is not entirely unexpected, given the fact that plasma naltrexone levels in the present study were equivalent to a relatively low dose of oral naltrexone.

There were few adverse events, other than an initial discomfort associated with the actual injections of depot naltrexone and mild soreness at the injection site for 2–3 days following the injections. Kranzler et al. (1998), who tested a single injection of the same formulation of depot naltrexone used in the present study, also noted that participants reported pain upon administration of depot naltrexone. In addition, these investigators reported that in 13 of 15 participants, an area of induration occurred at the injection site, which resolved over a period of 2.8 weeks (Kranzler et al. 1988). Induration was not found in the present study. Other negative side-effects typically reported after naltrexone administration are predominantly related to mood or gastrointestinal complaints (e.g. Hollister et al. 1981; Greenstein et al. 1984; Crowley et al. 1985; Shufman et al. 1994; Oncken et al. 2001), but these effects were not observed in the present study.

In addition to the discomfort associated with the injection itself, it is possible that depot naltrexone itself exacerbated withdrawal discomfort. The elevated SOWS scores in the high-dose group shown in Fig. 3 seem to provide support for this notion. However, this possibility is unlikely for a number of reasons. First, on the day prior to administration of 384 mg depot naltrexone, mean SOWS scores were 18.7 (± 9.0), and on the day that depot naltrexone was administered, mean scores were only

slightly higher at 20.8 (± 4.9). Therefore, depot naltrexone did not appear to exacerbate withdrawal in the high-dose group. SOWS scores in the low-dose group were also not different immediately before and after administration of depot naltrexone. Second, up to 50 mg oral naltrexone was administered for several consecutive days prior to administration of depot naltrexone. Given that 384 mg depot naltrexone produced blood levels of naltrexone comparable to approximately 12.5 mg oral naltrexone, it is unlikely that depot naltrexone would have exacerbated withdrawal. And finally, during a debriefing session at the end of the study, we specifically asked each participant whether he felt withdrawal symptoms after receiving the injections of depot naltrexone, and none claimed to experience any symptoms. Therefore, it is likely that the elevated SOWS scores in the high-dose group during the first week after administration of depot naltrexone reflects lingering baseline differences in withdrawal, rather than any direct effects of depot naltrexone. In a treatment setting where oral naltrexone may not be given prior to depot naltrexone administration, exacerbation of withdrawal could be avoided by lengthening the duration of the detoxification, and/or making ancillary medications, such as clonidine and benzodiazepines, available following administration of depot naltrexone.

In sum, the data presented in the current study demonstrate that this formulation of naltrexone produced a long-lasting antagonism of the effects of intravenous heroin, with minimal side-effects. Given that the primary difficulty associated with naltrexone maintenance in opioid abusers is medication compliance (Kosten and Kleber 1984; Fram et al. 1989; Preston et al. 1999), a formulation of naltrexone that requires only once-a-month administration has important and exciting treatment implications. Future studies in our laboratory will evaluate the clinical utility of depot naltrexone in the treatment of heroin dependence.

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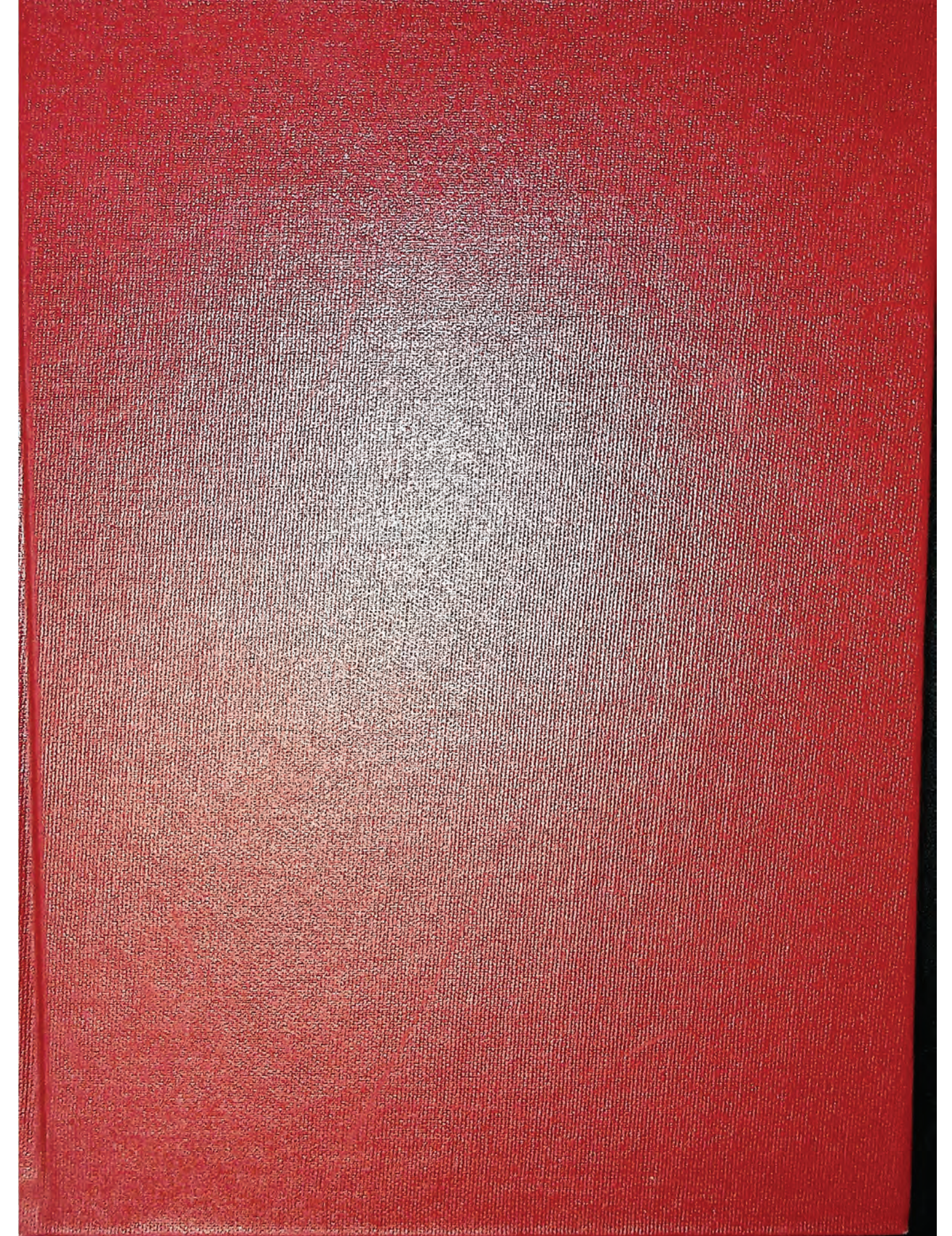
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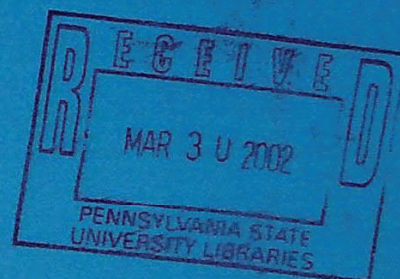
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Depot naltrexone: long-lasting antagonism of the effects of heroin in humans

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Abstract *Rationale:* Naltrexone, an opioid antagonist, is currently approved as a treatment for heroin dependence. However, naltrexone is generally not well accepted by patients, and medication non-compliance is a difficult obstacle to treatment. A sustained-release form of naltrexone may improve compliance. *Objective:* The present study was designed to evaluate the time course, safety, and effectiveness of a depot formulation of naltrexone (Depotrex®). *Methods:* Twelve heroin-dependent individuals participated in an 8-week inpatient study. After a 1-week detoxification period, six participants received 192 mg naltrexone base and six participants received 384 mg naltrexone base. For safety, the low dose of depot naltrexone was tested before the high dose. The effects of heroin (0, 6.25, 12.5, 18.75, 25 mg, IV) were evaluated for the next 6 weeks. One dose of heroin was tested per day on Mondays through Fridays, and the entire dose range was tested each week. Active heroin doses were administered in ascending order during the week, while placebo could be administered on any day. Subjective, performance, and physiological effects were measured both before and after heroin administration. The hypotheses were that depot naltrexone would antagonize the effects of heroin, and that the high dose of depot naltrexone would produce a more effective and longer-lasting antagonism than the low dose. *Results:* The low and high doses of depot naltrexone antagonized heroin-induced subjective ratings for 3 and 5 weeks, respectively. Plasma levels of naltrexone remained above 1 ng/ml for approximately 3 and 4 weeks after administration of 192 mg and 384 mg naltrexone. Other than the initial discomfort associated with the injection of depot

naltrexone, there were no untoward side-effects. *Conclusions:* These results suggest that this depot formulation of naltrexone provides a safe, effective, long-lasting antagonism of the effects of heroin.

Keywords Heroin · Human · Naltrexone · Opioid · Subjective effect · Sustained-release · Depotrex

Introduction

Naltrexone, an orally effective opioid antagonist, was approved in 1984 by the Food and Drug Administration as a maintenance medication for the treatment of heroin dependence. Naltrexone potently antagonizes the effects of opioid agonists, while producing no agonist effects of its own (Jaffe and Martin 1990). Tolerance does not develop to naltrexone's antagonist effects and the drug has few side effects, even after chronic administration of over 1 year (Kleber et al. 1985). Because of its ability to antagonize the effects of mu opioid agonists, its long duration of action, and its favorable pharmacokinetic and metabolic characteristics (Martin et al. 1966, 1973), naltrexone initially held great promise as a treatment for opioid dependence. The early rationale for using a pure antagonist was that once the individual was maintained on naltrexone, subsequent attempts to self-administer the illicit opioid would not produce euphoria (Wikler 1965; Martin et al. 1966) and the user would eventually discontinue opioid use altogether.

Although the use of naltrexone as a maintenance therapy for opioid abuse can be effective (Martin et al. 1973; O'Brien et al. 1975; Judson et al. 1981), it has been used most successfully with only a select subpopulation of highly motivated individuals. Because of the problems with medication non-compliance, naltrexone therapy has not lived up to its initial promise. This may be in part because opioid users are accustomed to self-administering potent reinforcers, and, by contrast, the complete absence of opioid-induced reinforcing effects may be unacceptable. Another factor that may contribute to noncom-

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Table 1 Participant demographics. Numbers in parentheses represent ± 1 SEM

	192 mg naltrexone	384 mg naltrexone
Age (average; years)	33.8 (2.5)	29.2 (3.2)
Years of heroin use (average)	10.7 (2.5)	9.1 (3.5)
Amount spent for heroin (average; \$/day)	\$39 (4)	\$55 (12)
Tobacco cigarette use (range; no. per day)	8–20	10–20
Cocaine use (range; occasions/week)	0–1	0–3
Amphetamine use (range; occasions/week)	0–1	0
Marijuana use (range; occasions/week)	0–1	0–3
Alcohol use (range; occasions/week)	0–1	0–3
Sedative use (range; occasions/week)	0–1	0–1

pliance is that, unlike methadone, discontinuation of naltrexone maintenance has no adverse consequences (e.g. withdrawal effects). Furthermore, naltrexone itself may induce adverse neuropsychiatric and gastrointestinal effects, such as dysphoria, nausea, and abdominal pain (Hollister et al. 1981; Crowley et al. 1985; Oncken et al. 2001).

Sustained-release forms of naltrexone could increase compliance and ultimately improve treatment effectiveness (Martin and Sandquist 1974; Abrahams and Ronel 1975; Chiang et al. 1985a, 1985b). Chiang et al. (1985a, 1985b), for example, administered biodegradable beads containing a dose of 63 mg naltrexone to normal, healthy volunteers. Following an initial burst of release, this formulation yielded relatively constant plasma levels of naltrexone (0.3–0.5 ng/ml) for up to 1 month. However, when these investigators administered challenge doses of morphine (15 mg IM), the results were variable. In some participants, morphine was completely ineffective, while in others, morphine-like effects were observed. In addition, three of the five participants who completed the study developed tissue inflammation near the site of bead implantation (Chiang et al. 1985b). Although the adverse tissue reaction and the variable antagonist effectiveness of the naltrexone beads limited its clinical utility, the rationale behind the development of a sustained-release form of naltrexone was sound.

A new depot formulation of naltrexone (Depotrex®) has been developed that provides a stable, long-lasting elevation in plasma naltrexone levels with either no or minimal side-effects (Heishman et al. 1994; Alim et al. 1995; Kranzler et al. 1998). In an early tolerability study, Alim and colleagues (1995) reported blockade of the physiological and subjective effects of 10 mg intravenous (IV) morphine in cocaine-dependent participants who received 206 mg depot naltrexone; side-effects associated with naltrexone were minimal in these participants. Kranzler and colleagues (1998) further showed that 206 mg depot naltrexone significantly reduced the percentage of heavy drinking days in alcoholics. Adverse effects reported after depot naltrexone were comparable to those reported after oral naltrexone administration. Although this formulation of depot naltrexone appears to be safe and effective in treating alcohol dependence, it has not yet been tested with heroin. The purpose of the current study was 1) to determine whether the new formulation of depot naltrexone will antagonize the effects

of heroin at doses comparable to those used on the streets today, and 2) to assess the duration of antagonist effect of 192 mg and 384 mg depot naltrexone. The hypothesis was that depot naltrexone would dose-dependently antagonize the effects of heroin.

Materials and methods

Participants

Fifteen heroin-dependent men, who were not seeking treatment for their drug use, began the 8-week protocol. Three participants left the study prior to depot naltrexone administration: one was discharged for aggressive behavior toward the staff, and two left for personal reasons. Twelve participants (eight non-Hispanic Caucasian, three Hispanic, and one African American) completed the study: six received 192 mg depot naltrexone, and six received 384 mg depot naltrexone (Table 1). The low dose of depot naltrexone was tested in the first six participants. The groups did not differ in age, years of heroin use, and amount of money spent on heroin per day. All participants had experience using heroin IV. One participant in the low-dose group and two in the high-dose group preferred to use heroin intranasally; all other participants preferred to use heroin IV. All participants were dependent on heroin at the start of the study, as verified by a naloxone challenge test (Wang 1974).

After an initial telephone interview, eligible participants completed detailed questionnaires on drug use, general health and medical history, and a medical and psychological evaluation in the laboratory. An electrocardiogram and Mantoux test or chest X-ray were also performed. Routine laboratory analyses included a blood chemistry panel, thyroid function test, syphilis and hepatitis (A, B, and C) screening, and urinalysis. Urine drug toxicologies (opioids, cocaine, benzodiazepines, cannabinoids, and amphetamines) were also performed using a radiative energy attenuation and fluorescence polarization immunoassay system (ADx System; Abbott Laboratories, Abbott Park, Ill., USA). Participants were told that they would be detoxified from heroin during the first week of the study, that they would receive one of two doses of a depot formulation of naltrexone, and that a range of IV heroin doses would be tested each week for the 6 weeks following depot naltrexone administration.

Participants were excluded from the study if they were seeking drug treatment, dependent on alcohol or illicit drugs other than opioids, or had a major Axis I psychiatric diagnosis other than opioid dependence. Those who had recent histories of violence or who were on parole/probation were excluded from the study. Participants were required to be physically healthy, and fully able to perform all study procedures. Although both men and women were screened for the study, none of the women met the eligibility requirements. Prior to admission, participants completed a training session, during which the study procedures were explained to them in detail. Volunteers were paid \$25 per inpatient day and an additional \$25 per day bonus if they completed the study. Participants signed consent forms describing the aims of the study, and

the potential risks and benefits of participation. Free HIV testing and education were offered, and during the last week of the study, participants were offered referrals for treatment. This study was approved by the Institutional Review Board of the New York State Psychiatric Institute (NYSPI).

Apparatus

During experimental sessions, participants were seated in a room equipped with Macintosh computers. All computer activities, vital signs and behaviors were continuously monitored by the experimenters in an adjacent control room via a continuous on-line computer network, video cameras, and vital signs monitors (cardiovascular function was measured using a Sentry II Vital Signs Monitor, NBS Medical, Costa Mesa, Calif., USA; arterial oxygen saturation was measured using a pulse oximeter Model 400, Palco Laboratories, Santa Cruz, Calif., USA). Communication between the staff and participants was kept to a minimum during experimental sessions.

Detoxification procedures

Participants were admitted into the hospital, and detoxified during the first week after admission. Buprenorphine (8 mg sublingual tablet; National Institute on Drug Abuse, Rockville, Md., USA) was administered on the first 1–2 days after admission. Two days after the last buprenorphine dose, oral naltrexone (DuPont Pharma, Wilmington, Del., USA) was administered for 3 consecutive days (25, 50, and 50 mg per day) to ensure that participants were willing and able to tolerate its effects. Clonidine HCl (0.2 mg PO, every 6 h; Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Conn., USA), ketorolac tromethamine (30 mg IM, every 6 h; Roche Laboratories, Nutley, N.J., USA), prochlorperazine (10 mg PO or IM, every 8 h; SmithKline Beecham Consumer Healthcare, Pittsburgh, Penn., USA) and clonazepam (2 mg PO, every 8 h; Roche Laboratories) were available, as needed, during the detoxification week. Thereafter, trazodone (50–100 mg PO, at bedtime; Warner Chilcott, Morris Plains, N.J., USA) was available if participants reported having trouble sleeping. Depot naltrexone was administered on a Monday morning, 2 days after the last oral naltrexone dose.

General procedures

The effects of IV heroin (placebo, 6.25, 12.5, 18.75, and 25 mg) were evaluated each week for 6 weeks following depot naltrexone administration. The entire dose range was tested each week, and one dose of heroin was tested each day on weekdays. For safety, active heroin doses were administered in ascending order within each week, with the exception that the day of placebo injection was varied across weeks. On the day that depot naltrexone was administered, placebo was tested during the experimental session.

Experimental sessions

During all sessions, participants completed computerized tasks and subjective-effects questionnaires. Heart rate and blood pressure were measured every 2 min, and blood oxygen saturation was monitored continuously with a pulse oximeter and recorded every minute during experimental sessions. Participants received breakfast between 0800 and 0900 and lunch between 1230 and 1330 hours. Experimental sessions occurred between 0930 and 1130 hours. Participants were not allowed to smoke tobacco cigarettes during experimental sessions.

Physiologic, subjective and performance effects were measured both before and after drug administration (see descriptions below). Heroin or placebo was administered only if vital signs were within safe limits ($SpO_2 > 93\%$). A photograph was taken of the right pupil before and 4, 10, 20, 40 and 60 min after drug ad-

ministration. The subjective-effects battery (see description below) was administered before and 4, 40 and 90 min after drug administration. The performance battery (see description below) was administered before and 10 and 60 min after drug administration. The Subjective Opioid Withdrawal Scale was administered before drug administration. The Drug Effects Questionnaire was administered 90 min after drug administration.

Subjective measures

Four questionnaires were used to assess subjective effects throughout the experimental sessions. The first questionnaire was a 26-item visual analog scale (VAS) designed to assess subjective and physiological effects (modified from Foltin and Fischman 1995). The first 18 lines were labeled with adjectives describing mood states (e.g., "I feel...:" "high") and four additional lines, labeled with questions about the dose just received (i.e., "I liked the dose," "For this dose, I would pay"). Participants also indicated, by making a mark along a 100 mm line, how much they "wanted" each of the following drugs: heroin, cocaine, alcohol, and tobacco. Participants rated each item on the VAS from "Not at all" (0 mm) to "Extremely" (100 mm), except for the "For this dose, I would pay" question, which ranged between \$0 (0 mm) to \$20 (100 mm). The second questionnaire was a 13-item opioid symptom checklist consisting of true/false questions designed to measure opioid effects (e.g., "My skin is itchy," etc.; Fraser et al. 1961; Foltin and Fischman 1992). The VAS and opioid symptom checklist together constituted the subjective-effects battery. The third questionnaire was the 16-item Subjective Opioid Withdrawal Scale (SOWS; Handelsman et al. 1987). Participants rated each item on a scale from 0 to 4, with 0 being "Not at all" and 4 being "Extremely" (e.g., "I have gooseflesh," etc.). The fourth questionnaire was a 6-item Drug Effects Questionnaire (DEQ; Evans et al. 1995). Participants described drug effects by selecting among a series of possible answers ranging from 0 ("No effects at all") to 4 ("Very strong (good, bad, etc.) effects"). Ratings of drug liking ranged between -4 ("Dislike very much") to 4 ("Like very much").

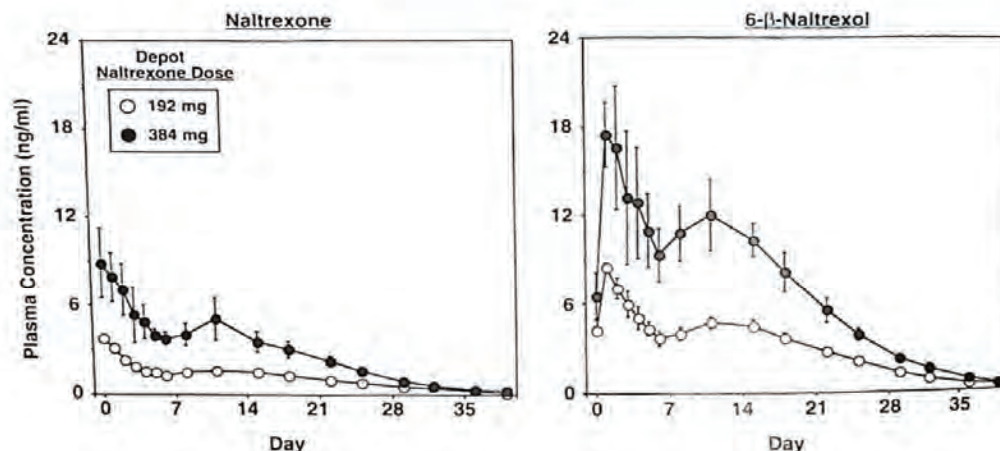
Task battery

The task battery consisted of four tasks: the first task was a 3-min digit-symbol substitution task, during which participants were required to emulate a series of patterns on a keypad (McLeod et al. 1982). The second task was a 10-min divided attention task, which consisted of concurrent pursuit-tracking and vigilance tasks (Miller et al. 1988). The third task was a 10-min rapid information processing task, during which a series of digits was displayed rapidly on the computer screen (100 digits/min), and participants were instructed to press a key as quickly as possible after three consecutive odd or even digits (Wesnes and Warburton 1983). The fourth task was a 3-min repeated acquisition of response sequences task, during which four buttons were illuminated, and participants were instructed to learn a ten-response sequence of button presses (Kelly et al. 1993).

Physiological measures

A blood pressure cuff was attached to the non-dominant arm, which recorded automatically every 2 min. Participants were also connected to a pulse oximeter via a soft sensor on a finger of the dominant hand, which monitored arterial blood oxygen saturation (SpO_2). For safety, supplemental oxygen (2 l/min) was provided via a nasal cannula during all experimental sessions. A specially modified Polaroid camera with a close-up lens ($\times 2$ magnification) was used to take pupil photographs. All photographs were taken under ambient lighting conditions. Horizontal and vertical measurements of pupil diameter were made using calipers, and then these two measurements were averaged and divided by 2 to correct for the $\times 2$ magnification.

Fig. 1 Mean plasma levels of naltrexone (left panel) and 6- β -naltrexol (right panel) as a function of depot naltrexone dose and days after administration of depot naltrexone. Data points represent the mean across 6 participants per group. Error bars represent ± 1 SEM



Blood was drawn 2 h, 1, 2, 3, 4, 5, 6, 8, 11, 15, 18, 22, 25, 29, 32, 36, and 39 days after administration of depot naltrexone, and immediately centrifuged at 3000 rpm for 15 min. Plasma was drawn off and stored at -20°C until it was shipped by overnight mail on dry ice for analyses of naltrexone and 6- β -naltrexol (Center for Human Toxicology, University of Utah, Salt Lake City, Utah, USA). Analyses were performed by solid phase extraction and negative ion chemical ionization gas chromatography/mass spectrometry, as described by Huang and colleagues (1997). The lower limit of detectability for both analytes was 0.1 ng/ml.

Blood was also drawn prior to, and at weekly intervals after administration of depot naltrexone for analyses of liver enzymes (AST, ALT, GGT).

Drugs

Depot naltrexone (Depotrex[®]) was manufactured by Biotek Inc. (Woburn, Mass., USA) and provided by the National Institute on Drug Abuse. Depotrex is a registered trademark of Biotek, Inc. Naltrexone microcapsules and placebo microspheres were packaged in sterile single-dose vials. After reconstituting in suspending medium, 2.4 ml of the suspension was injected. The active formulation contained drug equivalent to 192 mg naltrexone base. The placebo formulation contained the equivalent weight in polymer microspheres. Injections were administered subcutaneously into the buttocks (one injection per buttock), using an 18 gauge needle. For the low dose, participants received one placebo and one naltrexone injection (192 mg naltrexone base), and for the high dose, participants received two naltrexone injections (394 mg naltrexone base). For safety, the low dose of Depotrex was tested in the first six participants, and the high dose of Depotrex was tested in the next six participants.

Heroin HCl was provided by the National Institutes on Drug Abuse and prepared by the Columbia-Presbyterian Medical Center research pharmacy. A 25 mg/ml heroin concentration was prepared in a 5% dextrose solution to enhance stability. Dose calculations were based on the hydrochloride salt form. Heroin was stored in a freezer and used within 3 months of preparation. The stock solution was diluted in 5% dextrose to produce each dose. Placebo (5% dextrose solution) or heroin (6.25, 12.5, 18.75, and 25 mg) was administered intravenously over a 30-s period in a total volume of 2 ml. Heroin doses were administered in a double-blind fashion. Physiological saline solution was infused continuously during experimental sessions, except during drug administration. Between 1 and 2 ml heparinized saline (10 IU/ml) was flushed into the catheter four to eight times each day. All venous catheters were maintained as heparin locks and were removed within 72 h of insertion.

Supplemental medications available to all participants for the duration of the study included: Mylanta, acetaminophen, ibuprofen, Colace, Milk of Magnesia and multi-vitamins with iron.

Morning urine samples were collected daily and one random sample per week was screened for the presence of other illicit substances. No illicit substances were found in the participants' urine samples.

Statistical analyses

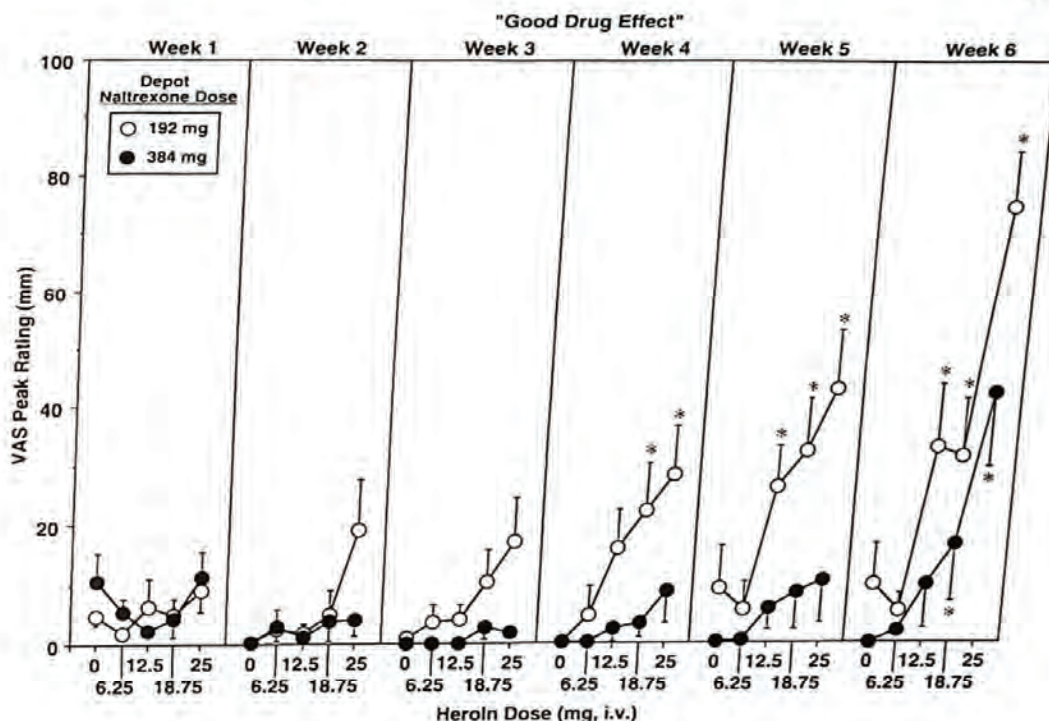
Repeated-measures analyses of variance (ANOVA) with planned comparisons were used to address the following questions: 1) What was the duration of antagonism of heroin's effects? 2) Did the low and high doses of depot naltrexone differ in ability to antagonize the effects of heroin? In order to address the first question, the data for each group were analyzed separately as a function of week (1–6) and heroin dose (0, 6.25, 12.5, 18.75, 25 mg). Twenty-five planned comparisons were made: each week (2–6) was compared to week 1 for each dose (e.g. placebo-week 2 versus placebo-week 1, placebo-week 3 versus placebo-week 1, placebo-week 4 versus placebo-week 1, etc.) because it was likely that virtually complete antagonism would occur during week 1. In order to address the second question, an overall analysis was performed with one between-group factor (group) and two within-group factors (week, heroin dose): the main effect of group, and the week $\times$ group and dose $\times$ group effects were evaluated. Interaction effects were examined using post-hoc comparisons. Peak subjective ratings, peak performance effects, trough pupil diameter, liver enzyme levels, average arterial oxygen saturation, and plasma levels of naltrexone and 6- β -naltrexol were analyzed. Liver enzymes (AST, ALT, GGT) were also analyzed: each week post-depot naltrexone was compared to a pre-depot naltrexone baseline. Due to an excessive number of missing data points, the cardiovascular data were not analyzed. To control for type I errors, a modified Bonferroni test was used in that only those comparisons with $P < 0.01$ were considered statistically significant.

Results

Plasma drug levels

Figure 1 shows mean plasma levels of naltrexone (left panel) and 6- β -naltrexol (right panel) for each group as a function of time since the depot naltrexone injection. Two hours after administration of 192 mg and 384 mg depot naltrexone, plasma levels of naltrexone were 3.8 (± 0.2) and 8.9 (± 1.4) ng/ml. Plasma levels of 6- β -naltrexol were 8.5 (± 0.3) and 17.4 (± 1.3) ng/ml, respectively, 24 h after administration of 192 mg and 384 mg depot naltrexone. Across individual participants, plasma levels

Fig. 2 Mean peak VAS ratings of "Good Drug Effect" after administration of heroin (0–25 mg) as a function of depot naltrexone dose and study week (week 1: left panel; week 6: right panel). Maximum rating=100 mm. Data points represent mean peak ratings ($n=6$ per group). Error bars represent ± 1 SEM. * Indicates significant differences from week 1



of naltrexone ranged between 3.1 and 4.5 ng/ml after administration of 192 mg depot naltrexone, and 5.6 and 14.2 ng/ml after administration of 384 mg depot naltrexone. After administration of 192 mg and 384 mg of depot naltrexone, plasma levels of naltrexone were less than 1 ng/ml on day 22 and 29, respectively. The group and group $\times$ day effects for naltrexone [group: $F(1,10)=48.5$, $P<0.0001$; group $\times$ day: $F(1,10)=8.6$, $P<0.0001$] and 6- β -naltrexol [group: $F(1,10)=33.8$, $P<0.0002$; group $\times$ day: $F(1,10)=8.3$, $P<0.0001$] were significant.

Subjective effects

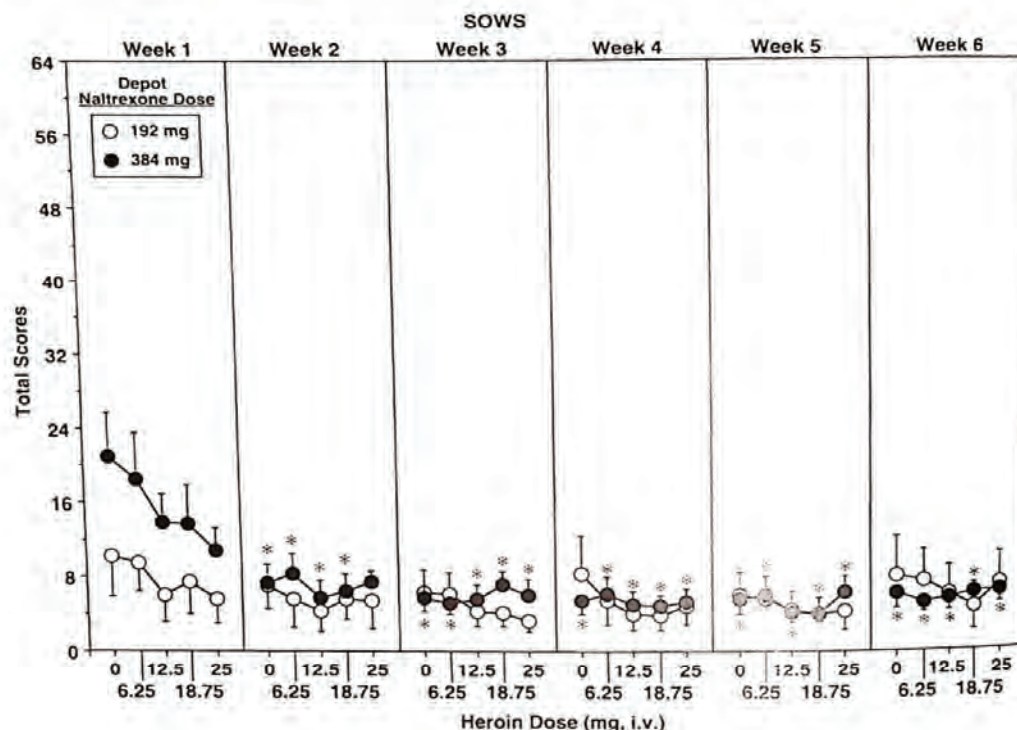
Figure 2 shows mean peak visual analog scale ratings of "Good Drug Effect" for each group as a function of heroin dose and week. After low-dose depot naltrexone, ratings of "Good Drug Effect" significantly increased by week 4, relative to week 1, after administration of 18.75 mg [$F(1,100)=6.4$, $P<0.01$] and 25 mg heroin [$F(1,100)=7.9$, $P<0.006$]; ratings of "Good Drug Effect" significantly increased by week 5 after administration of 12.5 mg heroin [$F(1,100)=8.4$, $P<0.004$]. In the high-dose group, ratings of "Good Drug Effect" did not significantly increase until week 6, after 18.75 mg [$F(1,100)=7.5$, $P<0.007$] and 25 mg heroin [$F(1,100)=47.3$, $P<0.0001$]. Both the week $\times$ group [$F(5,50)=4.8$, $P<0.001$] and dose $\times$ group [$F(4,40)=4.4$, $P<0.005$] effects were significant for ratings of "Good Drug Effect." Several other VAS ratings showed a similar pattern including ratings of "High," "Liking," drug "Potency," drug "Quality," and how much they would be willing to pay for the dose (data not shown). The dose $\times$ group

effect was significant [$F(4,40)=4.2$, $P<0.006$], and the week $\times$ group effect approached statistical significance [$F(5,50)=2.9$, $P<0.02$] for ratings of "High." Although ratings tended to be higher in the low-dose group for VAS ratings of "Liking," drug "Potency," and drug "Quality," the week $\times$ group and dose $\times$ group effects were not statistically significant for these items.

VAS ratings of "I feel..." "Gooseflesh," "Depressed," "Muscle Pain," "Anxious," and "Restless" were elevated in both groups during the first week after receiving depot naltrexone, and were higher in the high-dose group (data not shown). The week $\times$ group effect was statistically significant for ratings of "Gooseflesh" [$F(5,50)=3.4$, $P<0.01$] and "Depressed" [$F(5,50)=3.5$, $P<0.009$], while the week $\times$ group effect for ratings of "Muscle Pain" ($P<0.03$), "Anxious" ($P<0.04$), and "Restless" ($P<0.04$) approached statistical significance. Ratings of "I Want Heroin," which did not vary across study weeks or heroin doses, were significantly elevated in the high-dose group [main effect of group: $F(1,10)=26.3$, $P<0.0004$]. Ratings of "I Want Heroin" ranged between 26 and 37 in the low-dose group, and 86 and 95 in the high-dose group.

The pattern of results obtained from the opioid symptom checklist and DEQ (data not shown) were similar to the VAS ratings of "Good Drug Effect" (Fig. 2) in that total scores on the opioid symptom checklist and DEQ ratings of drug "Liking," "Good Drug Effect," strength of drug effect, and desire to take the drug again increased as a function of heroin dose and across study weeks. The week $\times$ group effect was statistically significant for the opioid symptom checklist [$F(5,50)=3.2$, $P<0.01$]. Although ratings tended to be higher in the

Fig. 3 Mean total scores on the Subjective Opioid Withdrawal Scale (SOWS) after administration of heroin as a function of depot naltrexone dose and study week. Maximum score=64. All other details are as in Fig. 2



low-dose group compared to the high-dose group, the week $\times$ group and dose $\times$ group effects were not statistically significant for any of the items on the DEQ.

Subjective ratings of opioid withdrawal, as measured by total scores on the SOWS, did not significantly differ between groups during detoxification, prior to administration of depot naltrexone. SOWS scores peaked on day 4 after admission: total SOWS scores on day 4 of withdrawal were 22.5 (± 11.2) and 26.3 (± 7.3), out of a maximum possible score of 64, after administration of 192 and 384 mg depot naltrexone, respectively. On the day prior to administration of depot naltrexone, SOWS scores were 11.0 (± 8.2) and 18.7 (± 9.0) in the low- and high-dose groups, respectively. Figure 3 shows total SOWS scores after administration of depot naltrexone for each group as a function of heroin dose and week. Total SOWS scores were significantly elevated during the first week in the high-dose group, but not in the low-dose group. By the second week after administration of depot naltrexone, SOWS scores did not differ between groups. The week $\times$ group interaction for total SOWS scores approached statistical significance [$F(5,50)=2.5$, $P<0.04$].

Performance tasks

Heroin minimally affected task performance, with the exception that performance of the divided attention task was significantly impaired: in the low-dose group, the latency to identify a target significantly increased by 1.7 s during week 5, relative to week 1, after administration of 25 mg heroin [$F(1,100)=8.3$, $P<0.005$]. In the high-dose group, the latency to identify a target significantly

increased by 1.3 s during week 6, relative to week 1, after administration of 25 mg heroin [$F(1,100)=30.9$, $P<0.0001$]. Latency to identify a target did not significantly change across weeks after administration of placebo in either group. The week $\times$ group and dose $\times$ group effects were not statistically significant for latency to identify a target during the divided attention task.

Physiological effects

Figure 4 shows the effects of heroin on pupil diameter for each group as a function of heroin dose and week. During week 1, pupil diameter was large in both groups, consistent with the possibility that both groups were in mild withdrawal. After placebo administration during week 1, pupil diameter was 5.3 (± 0.3) and 5.6 (± 0.6) mm in the low- and high-dose groups, respectively. Pupil diameter was relatively stable under the placebo condition in both groups from weeks 2–6 (Fig. 4), although pupil diameter consistently remained larger in the high-dose group throughout the study. After administration of active doses of heroin, pupil diameter progressively decreased across study weeks in both groups. The week $\times$ group and dose $\times$ group effects were not significant for pupil diameter.

The average arterial oxygen saturation significantly decreased by 0.9% in both groups from week 1 to week 6, after administration of 25 mg heroin [low-dose group: $F(1,100)=17.2$, $P<0.0001$; high-dose group: $F(1,100)=7.8$, $P<0.006$]. However, these changes in oxygen saturation occurred in the presence of supplemental oxygen, and were not clinically significant.

Fig. 4 Mean trough pupil diameter after administration of heroin as a function of depot naltrexone dose and study week. All other details are as in Fig. 2

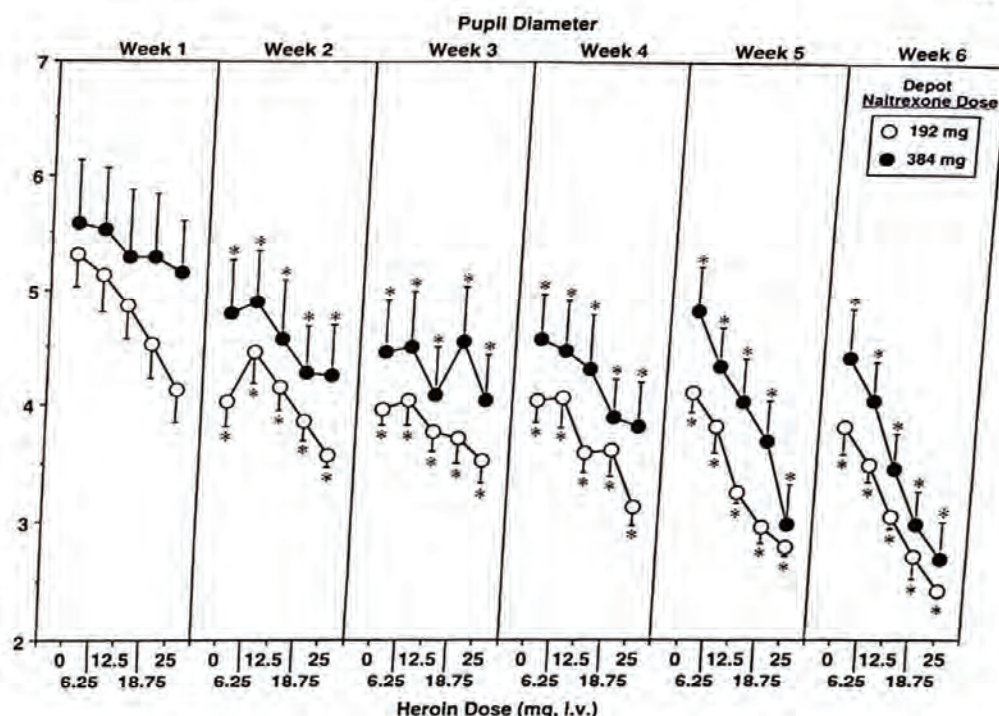


Table 2 ALT, AST, and GGT values (IU/l) at baseline and for 6 weeks following administration of 192 mg or 384 mg depot naltrexone. Numbers in parentheses represent ± 1 SEM. Asterisks represent significant differences from baseline ($P < 0.01$)

	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
192 mg							
ALT	29.2 (7.2)	54.7 (22.2)	63.3 (26.5)	65.3 (25.8)	75.2 (31.0)*	60.7 (21.4)	34.3 (6.3)
AST	19.7 (2.3)	27.8 (6.9)	31.2 (7.4)	26.8 (6.2)	34.7 (8.9)*	31.5 (7.8)	22.5 (3.1)
GGT	42.3 (17.5)	39.7 (14.6)	46.8 (14.6)	55.0 (18.4)*	62.3 (20.7)*	56.7 (18.0)*	45.7 (16.1)
384 mg							
ALT	24.3 (7.2)	132.3 (99.8)	51.8 (17.4)	45.5 (16.0)	50.0 (20.0)	53.3 (24.2)	49.0 (21.6)
AST	21.5 (3.7)	31.8 (5.9)	22.8 (4.8)	24.7 (5.5)	29.5 (6.5)	36.2 (11.8)	31.0 (6.8)
GGT	28.7 (9.7)	55.0 (24.0)	47.5 (16.4)	40.0 (11.7)	40.2 (12.1)	39.0 (11.3)	36.0 (11.3)

Liver enzyme (ALT, AST, GGT) values at baseline were within the normal range for all participants, with the exception of one individual in the low-dose group whose GGT value (128 IU/l) slightly exceeded the normal range of 5–80 IU/l. Three individuals in the low-dose group tested positive for hepatitis, and four individuals in the high-dose group tested positive for hepatitis. In the low-dose group, average GGT levels significantly increased during weeks 3, 4, and 5, relative to baseline [Tables 2; week 3: $F(1,30)=7.5$, $P < 0.01$; week 4: $F(1,30)=18.6$, $P < 0.0002$; week 5: $F(1,30)=9.6$, $P < 0.004$]. Both ALT [$F(1,30)=7.5$, $P < 0.01$] and AST [$F(1,30)=8.5$, $P < 0.007$] values in the low-dose group significantly increased during week 4, relative to baseline. Although these liver enzyme values following administration of the low dose were statistically significant, it is important to note that they were not clinically significant. The increases in liver enzyme values in the low-dose group were predominantly due to one hepatitis-negative individual: his baseline

GGT value was 54 IU/l, which peaked at 226 IU/l during week 4, and returned to 54 IU/l by week 6. Liver enzyme levels did not significantly change across study weeks in the high-dose group. The non-significant, transient increase in ALT values during week 1 in the high-dose group was due to one individual who received several doses of ketorolac tromethamine during detoxification. His liver enzyme levels peaked at 630 IU/l during week 1, and returned to normal (32 IU/l) by week 3.

Side-effects

Eleven of 12 participants reported pain during administration of the depot injections. These individuals reported no discomfort while standing, and only mild discomfort at the injection sites while seated, during the first 48–72 h after the injections. There was no evidence of induration, erythema, or irritation. One participant who

inadvertently received one of the injections (placebo) intramuscularly reported pain on that side for the first 72–96 h after the injection.

Discussion

The depot formulation of naltrexone used in the current study provided a safe, effective, long-lasting antagonism of the effects of heroin. Across the time points measured, the highest naltrexone plasma levels attained after administration of 192 mg and 384 mg of depot naltrexone were $3.8 (\pm 0.2)$ and $8.9 (\pm 1.4)$ ng/ml, respectively. For comparison, Walsh et al. (1996) reported that daily administration of 50 mg oral naltrexone resulted in naltrexone plasma concentrations of approximately 30 ng/ml, while daily administration of 12.5 mg oral naltrexone resulted in naltrexone plasma concentrations of approximately 10 ng/ml (plasma samples were collected 30 min after administration of naltrexone). Therefore, the amount of drug found in plasma after depot naltrexone administration is lower than the amount found after a standard dose of naltrexone used clinically for treating heroin dependence (50 mg/day).

In the present study, antagonism of heroin's effects occurred, despite negligible plasma levels of naltrexone. An early study conducted by Vereby and colleagues (Vereby et al. 1976) showed that 100 mg oral naltrexone did not completely antagonize the effects of 25 mg IV heroin when plasma levels of naltrexone fell below approximately 2 ng/ml. In contrast, Navaratnam and colleagues (Navaratnam et al. 1994) showed that after discontinuation of day 1-day 3-day 5 dosing with 100–100–150 mg oral naltrexone, antagonism of the effects of 25 mg IV heroin continued to occur when plasma levels of naltrexone were negligible. Schuh and colleagues (Schuh et al. 1999) also demonstrated that during a "wash-out period" after discontinuation of daily administration of 100 mg oral naltrexone, antagonism of the effects of up to 4 mg IM hydromorphone continued to occur when plasma levels of naltrexone were negligible. The data presented in the current study were more consistent with those of Navaratnam et al. (1994) and Schuh et al. (1999) in that 384 mg depot naltrexone antagonized heroin-induced ratings of "I Feel High" and "I Feel a Good Drug Effect" for up to 5 weeks, even though plasma levels of naltrexone were quite low (0.3 ± 0.04 ng/ml). These data are not entirely surprising, given a previous study demonstrating that the percentage blockade of [^{11}C]carfentanil binding in the brain of normal healthy volunteers at 48, 72, 120, and 168 h after administration of 50 mg oral naltrexone was 91, 80, 46, and 30%, respectively (Lee et al. 1988). Results from the Lee et al. (1988) study suggest that orally delivered naltrexone continues to inhibit brain opioid receptors in the absence of measurable plasma levels of naltrexone. In the present experiment, it is also possible that 6- β -naltrexol, the active metabolite of naltrexone, contributed to the continued antagonism of heroin's effects, particularly

because plasma levels of this metabolite were consistently higher than naltrexone throughout the study.

In the present study, both doses of depot naltrexone initially antagonized the positive subjective effects of heroin, consistent with naltrexone's well-established effectiveness in blocking the subjective effects of opioid agonists (e.g. Altman et al. 1976; Mello et al. 1980; Preston and Bigelow 1993; Schuh et al. 1999). Although the present study clearly demonstrated a long-lasting antagonism of the subjective effects of up to 25 mg IV heroin, it did not address the question of what dose of heroin would effectively override the blockade during the first few weeks after administration of depot naltrexone. In previous studies in our laboratory, participants who were maintained on morphine reported that 25 mg heroin was roughly equivalent to one \$10 "street bag" of heroin. Given that participants typically use between one and 2 bags of heroin per occasion, the effects of higher doses of heroin during the early weeks of the study would have provided useful information. However, because the present experiment was a late phase 1 study, and we did not have information regarding the duration of antagonism of opioid effects, we chose not to test higher heroin doses because of safety concerns. In addition, because of uncertainty about the effects of 25 mg heroin in non-dependent individuals, we chose to administer active heroin doses in ascending order in the present study. Therefore, order effects could have influenced responses on our outcome measures. Future studies will evaluate higher doses of heroin in the early weeks following administration of depot naltrexone, and heroin doses will be administered in non-systematic order.

One interesting finding in the present study was a dramatic difference in ratings of "I Want Heroin" in the low-dose group, relative to the high-dose group. Participants in the low-dose group had consistently lower scores for this item across study weeks and heroin doses. The differences in wanting heroin were perhaps related to the possibility that participants in the high-dose group were experiencing greater withdrawal. Consistent with this notion is the fact that throughout the study, pupil diameter was larger in the high-dose group, compared to the low-dose group. However, one argument against this possibility is that subjective ratings of withdrawal were negligible, and did not differ between groups from study weeks 2–6. In clinical settings, it is generally accepted that craving for heroin is reduced during the early weeks after treatment is initiated, perhaps due to a perception that heroin is unavailable under antagonist maintenance (e.g. Mirin et al. 1976; Hollister et al. 1977; Sideroff et al. 1978; Judson et al. 1981). However, it is interesting to note that in one clinical study comparing 60 and 120 mg thrice-weekly administration of oral naltrexone, craving for heroin increased in both groups during weeks in which heroin was used, but the increase in craving was significantly greater in the 120 mg group (Judson et al. 1981). As in the present study, Judson et al. (1981) had no clear explanation for why craving was greater in the group maintained on the higher dose of naltrexone.

Future studies are needed to evaluate more systematically the effects of depot naltrexone on craving for heroin. A possible theory may relate to the effects of the higher dose of naltrexone on endogenous ligands, such as endorphin.

Another issue that warrants attention is the effect of depot naltrexone on liver enzymes. The package insert for oral naltrexone warns of an increased risk of hepatocellular injury. Given the high rate of hepatitis in intravenous drug abusers, combined with the possibility that naltrexone itself may produce hepatocellular injury, we carefully monitored liver enzymes throughout the study, and only admitted participants whose liver enzymes were within the laboratory normal range at baseline. Under these conditions, depot naltrexone did not produce clinically significant increases in liver enzyme levels. These results were consistent with several studies demonstrating a lack of effect of naltrexone on liver functioning, even after daily administration of high doses of naltrexone (100–350 mg; Brahen et al. 1988; Sax et al. 1994; Marrazzi et al. 1997). In fact, liver enzyme levels actually decreased in alcoholics who were treated with 50 mg per day of oral naltrexone, presumably due to the fact that they were drinking less alcohol (Volpicelli et al. 1997). Similarly, a previous study of depot naltrexone in the treatment of alcoholics showed that liver enzyme values decreased (Kranzler et al. 1998). Therefore, it appears that the formulation of naltrexone used in the present study has minimal effects on liver functioning, which is not entirely unexpected, given the fact that plasma naltrexone levels in the present study were equivalent to a relatively low dose of oral naltrexone.

There were few adverse events, other than an initial discomfort associated with the actual injections of depot naltrexone and mild soreness at the injection site for 2–3 days following the injections. Kranzler et al. (1998), who tested a single injection of the same formulation of depot naltrexone used in the present study, also noted that participants reported pain upon administration of depot naltrexone. In addition, these investigators reported that in 13 of 15 participants, an area of induration occurred at the injection site, which resolved over a period of 2.8 weeks (Kranzler et al. 1988). Induration was not found in the present study. Other negative side-effects typically reported after naltrexone administration are predominantly related to mood or gastrointestinal complaints (e.g. Hollister et al. 1981; Greenstein et al. 1984; Crowley et al. 1985; Shufman et al. 1994; Oncken et al. 2001), but these effects were not observed in the present study.

In addition to the discomfort associated with the injection itself, it is possible that depot naltrexone itself exacerbated withdrawal discomfort. The elevated SOWS scores in the high-dose group shown in Fig. 3 seem to provide support for this notion. However, this possibility is unlikely for a number of reasons. First, on the day prior to administration of 384 mg depot naltrexone, mean SOWS scores were 18.7 (± 9.0), and on the day that depot naltrexone was administered, mean scores were only

slightly higher at 20.8 (± 4.9). Therefore, depot naltrexone did not appear to exacerbate withdrawal in the high-dose group. SOWS scores in the low-dose group were also not different immediately before and after administration of depot naltrexone. Second, up to 50 mg oral naltrexone was administered for several consecutive days prior to administration of depot naltrexone. Given that 384 mg depot naltrexone produced blood levels of naltrexone comparable to approximately 12.5 mg oral naltrexone, it is unlikely that depot naltrexone would have exacerbated withdrawal. And finally, during a debriefing session at the end of the study, we specifically asked each participant whether he felt withdrawal symptoms after receiving the injections of depot naltrexone, and none claimed to experience any symptoms. Therefore, it is likely that the elevated SOWS scores in the high-dose group during the first week after administration of depot naltrexone reflects lingering baseline differences in withdrawal, rather than any direct effects of depot naltrexone. In a treatment setting where oral naltrexone may not be given prior to depot naltrexone administration, exacerbation of withdrawal could be avoided by lengthening the duration of the detoxification, and/or making ancillary medications, such as clonidine and benzodiazepines, available following administration of depot naltrexone.

In sum, the data presented in the current study demonstrate that this formulation of naltrexone produced a long-lasting antagonism of the effects of intravenous heroin, with minimal side-effects. Given that the primary difficulty associated with naltrexone maintenance in opioid abusers is medication compliance (Kosten and Kleber 1984; Fram et al. 1989; Preston et al. 1999), a formulation of naltrexone that requires only once-a-month administration has important and exciting treatment implications. Future studies in our laboratory will evaluate the clinical utility of depot naltrexone in the treatment of heroin dependence.

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