

PGR2026-00015
U.S. Patent 12,245,997

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ATOSSA THERAPEUTICS, INC.,
Petitioner

v.

JINA PHARMACEUTICALS, INC.,
Patent Owner

PGR2026-00015
Patent 12,245,997

**EXPERT DECLARATION OF JUNE ANN MUNFORD IN
SUPPORT OF PETITION FOR POST-GRANT REVIEW OF
U.S. PATENT NO. 12,245,997**

1. My name is June Ann Munford. I am over the age of 18 and unless otherwise indicated, I have personal knowledge of the facts set forth herein, and am competent to testify to the same. All statements made herein made of my own knowledge are true and all statements made on information and belief are believed to be true. If called upon to do so, I would testify competently thereto.

2. I have been retained on behalf of the Petitioner to provide assistance in the above-captioned 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.

3. 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.

4. 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.

5. 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.

6. 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.

7. I have reviewed EX1004, "Endoxifen, a New Treatment Option for Mania: A Double-Blind, Active-Controlled Trial Demonstrates the Antimanic Efficacy of Endoxifen" by A. Ahmad, et al. as published in CTS: Clinical and Translational Science October 2016.

8. Attached hereto as Appendix AHMAD01 is a true and correct copy of the MARC record for CTS: Clinical and Translational Science 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 AHMAD01 accurately describes the title, publisher and ISSN number of CTS: Clinical and Translational Science. The Showing Results field present on page 3 of this record indicates the library's collection includes the October 2016 issue of CTS: Clinical and Translational Science containing "Endoxifen, a New Treatment Option for Mania: A Double-Blind, Active-Controlled Trial Demonstrates the Antimanic Efficacy of Endoxifen."

9. Attached hereto as Appendix AHMAD02 is a true and correct copy of "Endoxifen, a New Treatment Option for Mania: A Double-Blind, Active-Controlled Trial Demonstrates the Antimanic Efficacy of Endoxifen" as published

in CTS: Clinical and Translational Science as held by the Penn State University Library. I secured this PDF, which is the copy held by the Penn State University Library that corresponds to the MARC record in Appendix AHMAD01, from the library's collection. In comparing EX1004 to Appendix AHMAD02, it is my determination that EX1004 is a true and correct copy of "Endoxifen, a New Treatment Option for Mania: A Double-Blind, Active-Controlled Trial Demonstrates the Antimanic Efficacy of Endoxifen" by A. Ahmad, et al. as published in CTS: Clinical and Translational Science. Page 1 of Appendix AHMAD02 indicates this paper was first available via the ASCPT platform as of June 27, 2016, published in the October 2016 edition of the journal and corrected as of March 15, 2017.

10. The 008 field of the MARC record in Appendix AHMAD01 indicates the date of record creation. The 008 field of Appendix AHMAD01 indicates the Penn State University Library first acquired CTS: Clinical and Translational Science as of June 12, 2008 and held the journal in perpetuity until the publication of "Endoxifen, a New Treatment Option for Mania: A Double-Blind, Active-Controlled Trial Demonstrates the Antimanic Efficacy of Endoxifen." Considering this information, it is my determination that CTS: Clinical and Translational Science October 2016 and therefore "Endoxifen, a New Treatment Option for Mania: A Double-Blind, Active-Controlled Trial Demonstrates the Antimanic Efficacy of

Endoxifen” was made available to the public, including by the Penn State University Library, shortly after its initial publication as of June 27, 2016 and certainly no later than the date of correction on March 15, 2017.

11. Additionally, the library’s subscription history (from June 2008 through March 2017) and the volume information on the first page of Appendix AHMAD02 (Volume 9, Issue 5) indicate that CTS: Clinical and Translational Science is a regularly published periodical (as shown in Appendix AHMAD03, in 2016 and 2017, CTS: Clinical and Translational Science was published every other month).

12. Other fields in the MARC record provide terms that would have been searchable by interested parties to locate EX1004.

13. I have been warned that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of the patent at issue in this proceeding. I declare under penalty of perjury that the foregoing is true and correct.

Dated: December 10, 2025



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 (Case No. IPR2018-001281, 39521-00421IP, IPR2018-01282 and 39521-00421IP2)

2019 ● Erise IP

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

2019 ● Perkins-Coie

Adobe Inc. v. RAH Color Technologies LLC (Case No. 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 (Case No. IPR2020-1449)

2022 • Perkins-Coie
Realtek v. Future Link (Case No. IPR2021-01182)

2023 • Fish & Richardson
Neuroderm Ltd. v. Abbvie, Inc (Case No. PGR2022-00040)

2023 • Fish & Richardson
Nearmap US Inc. v. Pictometry International Corp. (Case No. 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. (Case No. 4:21-cv-149-ALM)

2024 • Willkie-Farr
Netflix, Inc. v. VideoLabs. Inc. (Case No. IPR2023-00628)

2024 • Quinn Emanuel Urquhart & Sullivan
Purdue University v. Wolfsped (Case No. 1:21-CV-840)

2024 • Fish & Richardson
Dish Network v. Entropic Communications (Case No. IPR2024-00393)

2025 • Perkins Coie

Amazon.com, Inc. v. Nokia Technologies Oy (Case No. IPR2024-00572)

2025 • Fish & Richardson

Dish Network v. Entropic Communications (Case No. IPR2024-00373)

Limited Case and Clientele History

Alston & Bird

- Ericsson

v. Collision Communications (Case No. IPR2022-01233)

- Nokia

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

- Universal Electronics Inc

v. Roku Inc (Case No. IPR2022-00818)

Alavi & Anaipakos PLLC

- Stingray Group Inc. and Stingray Music USA, Inc.

v. Edwin A. Hernandez-Mondragon and Egla Corp. (Case No. 1:24-cv-21226-RAR)

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)

Buchanan, Ingersoll & Rooney PC

- Google LLC, AT&T Service Inc., T Mobile USA Inc., Cellco Partnership, Ericsson Inc. & Nokia of America Corp.

v. KT Corp & Pegasus Wireless Innovation LLC (Case No. IPR2025-00293)

Deschert LLP

- Smaxtec Animal Care

v. ST Reproductive Technologies, LLC (Case No. IPR2024-00885)

Duane Morris

- Kangxi Communication Technologies

v. Skyworks Solutions Inc. (Case No. IPR2025-00373)

- Microsoft

v. Edge Networking Systems LLC (Case No. 1:24-cv-00215)

Erise I.P.

- Apple

v. Ericsson Inc. (Case No. IPR2022-00715)

v. Future Link Systems (Case No. IPRs 6317804, 6622108, 6807505, and 7917680)

v. INVT (Case No. 20-1881)

v. Navblazer LLC (Case No. IPR2020-01253)

v. Qualcomm (Case No. IPR2018-001281, 39521-00421IP, IPR2018-01282, 39521-00421IP2)

- v. Quest Nettech Corp (Case No. 2:19-cv-00118-JRG)
- v. Telefonaktiebolaget LM Ericsson (Case No. IPR2022-00275)
- v. Theta IP, LLC (Case No. IPR2024-00818)
- v. THL Holding Company LLC (Case No. 1:23-cv-00548)

- 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 (Case No. 2:18-cv-53-JRG)

- Sony Interactive Entertainment LLC

- v. Bot M8 LLC (Case No. IPR2020-01288)
 - v. Infernal Technology LLC (Case No. 2:19-CV-00248-JRG)

- Tesla

- v. Charge Fusion Technologies LLC (Case No. IPR2025-00032)

- Unified Patents

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

Fish & Richardson

- Apple

- v. AliveCor (Case No. 3:21-cv-03958)
 - v. LBS Innovations (Case No. 2:19-cv-00119-JRG-RSP)
 - v. Koss Corporation (Case No. IPR2021-00305)

v. Masimo (Case No. IPR 50095-0012IP1, 50095-0012IP2, 50095-0013IP1, 50095-0013IP2, 50095-0006IP1, 50095-0135IP1)

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

v. Qualcomm (Case No. IPR2018-001281, 39521-00421IP, IPR2018-01282, 39521-00421IP2)

v. Resonant Sys. (Case No. 7:23-cv-00077-ADA)

- AsusTek Computer Inc.

v. Videolabs, Inc. (Case No. 22-CV-00720-ADA)

- Dell

v. Neo Wireless (Case No. IPR2022-00616)

- Dish Network

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

v. Entropic Communications LLC (Case No. IPR2024-00393)

v. Realtime Adaptive Streaming (Case No. 1:17-CV-02097-RBJ)

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

- Evapco Dry Cooling

v. SPG Dry Cooling (Case No. IPR2021-00688)

- Genetec

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

- Huawei

v. Bell Northern Research LLC (Case No. 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)
- MediaTek
 - v. MOSAID (Case No. IPR2024-00718)
- Metaswitch
 - v. Sonus Networks (Case No. IPR2018-01719)
- Microsoft
 - v. Throughputer Inc (Case No. IPR2022-00757)
- Mom Enterprises
 - v. Ddrops Company (Case No. 1:22-cv-00332)
- MLC Intellectual Property
 - v. MicronTech (Case No. 3:14-cv-03657-SI)
- Nearmap Inc
 - v. EagleView Technologies (Case No. IPR2022-01009)
- Neuroderm Ltd.
 - v. Abbvie, Inc (Case No. PGR2022-00040)
- Posco Co Ltd.
 - v. Pascal Drillet et al. (Case No. IPR2025-00370)
- Realtek Semiconductor
 - v. Future Link (Case No. IPR2021-01182)

- Quectel

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

- Samsung

- v. Aire Technology (Case No. IPR2022-00877)

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

- v. Communication Technologies Inc (Case No. IPR2022-01221)

- v. Jawbone Innovations (Case No. IPR2022-00865)

- v. MemoryWeb LLC (Case No. IPR2022-00885)

- v. Dodots Licensing Solutions (Case No. IPR2023-00701)

- v. Telefonaktiebolaget LM Ericsson (Case No. IPR2021-00615)

- Texas Instruments

- v. Vantage Micro LLC (Case No. IPR2020-01261)

- Xilinx

- v. Sentient Sensors LCC (Case No. 1:22-cv-00173)

Goodwin Proctor

- Intel

- v. Proxense, LLC (Case No. 6:24-cv-00283)

- Samsung Electronics

- v. Mobile Data Technologies (Case No. 2:24-cv-00435)

- Taiwan Semiconductor Manufacturing Company Ltd.

- v. Advanced Integrated Circuit Process LLC (Case No. 2:24-cv-00623)

Groombridge Wu

- Nearmap

v. Eagle View Technologies Inc. and Pictometry International Corp. (Case No. 2:21-cv-00283-TS-DAO)

Irell & Manella

- Curium

Latham & Watkins LLP

- Apple

v. Advanced Coding Research LLC

Leydig, Voit & Mayer, Ltd.

- Public Availability Consultancy

O'Melveny & Myers

- Apple

v. Maxell (Case No. 5:19-cv-00036-RWS)

- Disney Media & Entertainment Distribution LLC

v. Digital Media Technology Holdings, LLC (Case No. 2:22-cv-01642)

- Micron Technology Inc.

v. Besang Inc (Case No. IPR2023-00900)

- Samsung

v. Daedalus Prime LLC (1335 Investigation)

Perkins-Coie

- Amazon
 - v. Nokia (Case No. IPR2024-00847 and IPR2024-00848)
 - v. Nokia Technologies Oy (Case No. IPR2024-00572)
- Heru Industries
 - v. The UAB Research Foundation (Case No. IPR2022-01148)
- Intel Corporation
 - v. BeSang Inc. (Case No. IPR2023-00991)
 - v. BitMICRO (Case No. 5:23-cv-00625)
 - v. Telefonaktiebolaget L M Ericsson (Case No. IPR2024-00610)
- Realtek Semiconductor
 - v. Future Link (Case No. IPR2021-01182)
- r-pac
 - v. Adasa, Inc. (Case No. 1:2024cv06102)
- Twitter Inc
 - v. VOIP-Pal.com (Case No. 3:20-cv-02397-JD)
- TCL Industries
 - v. Koninklijke Philips NV (Case No. IPR2021-00495, IPR2021-00496 and IPR2021-00497)
- VusionGroup
 - v. Hanshow (Case No. IPR2024-00857)

Pillsbury Winthrop Shaw Pittman

- Intel

v. FG SRC LLC (Case No. 6:20-cv-00315)

- Gravel Rating Systems

v. Costco (Case No. 4:21-cv-149)

v. Lowe's Home Centers (Case No. 4:21-cv-150)

v. T-Mobile USA (Case No. 4:21-cv-152)

v. Kohl's Inc. (Case No. 4:21-cv-258)

v. Under Armor (Case No. 4:21-cv-356)

Quinn Emanuel

- Exact Sciences Corporation

v. Geneoscopy, Inc. (Case No. IPR2024-00459 and IPR2024-1330)

- ServiceNow, Inc.

v. InQuisient, Inc. (Case No. 22-900-CJB)

- Wolfspeed

v. The Trustees of Purdue University (Case No. 1:2021-cv-00840)

Sheppard, Mullin, Richter & Hampton LLP

- Advanced Micro Devices, Inc and Pensando Systems, Inc.

v. Concurrent Ventures LLC and Xtreamedge, Inc. (Case No. IPR2025-00478)

- Cadence Design Systems Inc.

v. Semiconductor Design Technologies (Case No. 3:23-cv-01001)

Shook, Hardy & Bacon LLP

- HP Inc.

v. Universal Connectivity Technologies (Case No. 1:23-cv-01177)

Stern, Kessler, Goldstein & Fox

- Preliminary Research

Wilmer, Cutler, Pickering, Hale and Dorr

- Apple

v. Shunock (Case No. 1:23-cv-08598)

- Quest Diagnostics Inc., Haystack Oncology Inc. and Haystack Oncology GmbH

v. Natera, Inc. (Case No. 1:23-cv-08598)

- Roche Diabetes, Inc.

v. Trividia Health, Inc. (Case No. 1:24-cv-00668)

Willkie, Farr & Gallagher LLP

- Lenovo, Dell, HP

v. Universal Connectivity Technologies Inc. (Case No. 2:2023cv00449)

- Neurent

v. The Foundry, LLC (Case No. IPR2024-00669)

- Netflix, Inc.

v. VideoLabs, Inc. (Case No. IPR2023-00628)

APPENDIX AHMAD01

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019 a | DO NOT EDIT this 360 MARC RECORD

022 a | 1752-8062 y | 1752-8054

035 a | (WaSeS)ssj0063685

040 a | PFM b | eng e | pn c | PFM d | PFM d | CUS d | DLC d | HEBIS d | CASUM d | OCLCQ d | OCLCF d | SERSO d | EUW d | OCLCO d | DLC d | OCLCQ d | OCLCO d | COO d | WY@ d | OCLCQ d | VT2 d | NJT d | SFB d | OCLCQ d | OCLCO d | UBY d | OCLCO d | OCLCQ d | UAB d | AUD d | OCLCA d | WaSeS

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050 0 0 a | R850.A1

060 0 0 a | W1 b | CL665

245 0 0 a | Clinical and translational science h | [electronic resource].

246 1 3 a | CTS

246 1 i | Issues from some providers have title: a | Clin translational sci

260 3 | 2008- : a | [Oxford, UK] : b | Blackwell Pub., c | 2008-

260 3 | <2015-> : a | Hoboken, NJ : b | John Wiley & Sons

310 a | Bimonthly

362 1 a | Began with vol. 1, issue 1 (May 2008).

538 a | Mode of access: World Wide Web.

588 0 a | Vol. 1, issue 1 (May 2008); title from issue table of contents page (Blackwell Synergy Web site, viewed June 12, 2008).

588 1 a | Vol. 14, issue 6 (Dec. 2021) (Wiley Online Library viewed December 15, 2021).

650 0 a | Clinical medicine x | Research v | Periodicals.

650 0 a | Medicine, Experimental v | Periodicals.

650 0 a | Human experimentation in medicine v | Periodicals.

650 1 2 a | Clinical Medicine

650 1 2 a | Research

650 1 2 a | Translational Research, Biomedical.

650 2 2 a | Biomedical Research

655 0 a | Electronic journals.

776 0 8 i | Print version: t | Clinical and translational science x | 1752-8054 w | (DLC) 2008247775 w | (OCoLC)232647820

856 4 0 u | http://5K8E54MC2L.search.serialssolutions.com/?V=1.0&L=5K8E54MC2L&S=|Cs&C=CLATS&T=marc

910 a | CONSER online

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949 a | Electronic resource w | ASIS c | 1 i | 49126751-1001 i | ONLINE m | ONLINE r | Y s | Y t | ONLINE u | 10/18/2025 o | .STAFF. 360 MARC



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Report an Issue



Clinical and translational science [electronic resource].

Additional Titles

CTS and Issues from some providers have title: Clin translational sci

Published

2008- : [Oxford, UK] : Blackwell Pub., 2008-
<2015-> : Hoboken, NJ : John Wiley & Sons

Access Online

serialssolutions.com

Dates of Publication and/or Sequential Designation

Began with vol. 1, issue 1 (May 2008).

Subject(s)

[Clinical medicine—Research—Periodicals](#)[Medicine, Experimental—Periodicals](#)[Human experimentation in medicine—Periodicals](#)[Clinical Medicine](#)[Research](#)[Translational Research, Biomedical](#)[Biomedical Research](#)

Genre(s)

[Electronic journals](#)

ISSN

1752-8062

Publication Frequency

Bimonthly

Technical Details

Mode of access: World Wide Web.

[View MARC record](#) | catkey: 49126751

PennState

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Showing results 1 through 1 of 1

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Refine Results: [All](#) | [Journals Only](#) | [Books Only](#) | [Videos Only](#)

Limit by: [Peer Reviewed](#) | [Open Access](#)

Clinical and translational science

ISSN: 1752-8054

Peer Reviewed Open Access

2008 to Present in [PubMed \(Medline\)](#)

[Wiley Free Content](#)

[Wiley Online Library All Journals](#)

2008 to 2015 in [Wiley Journal Database \(BTAA\)](#)

04/01/2008 to Present in [Academic Search Complete \(Ebsco\)](#)

2016 to Present in [DOAJ Directory of Open Access Journals](#)

Search inside this journal

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Interlibrary Loan

Teaching Support for Instructors

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Collections

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Diversity

News and Events

Your Donation at Work

Libraries Calendar

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In Person

By Email

Schedule a Research Appt.

FAQs (or How Do I?..)

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ARTICLE

Endoxifen, a New Treatment Option for Mania: A Double-Blind, Active-Controlled Trial Demonstrates the Antimanic Efficacy of Endoxifen **Correction(s) for this article**

Corrigendum

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A Ahmad, S Sheikh, T Shah, MS Reddy, BSV Prasad, KK Verma, BB Chandrakant, M Paithankar, P Kale, RV Solanki, R Patel, H Barkate, I Ahmad

First published: 27 June 2016 | <https://doi.org/10.1111/cts.12407> | Citations: 23

SECTIONS

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Abstract

The protein kinase C (PKC) signaling system plays a role in mood disorders and PKC inhibitors such as endoxifen may be an innovative medicine for bipolar disorder (BP) patients. In this study we show for the first time the antimanic properties of endoxifen in patients with bipolar I disorder (BPD I) with current manic or mixed episode. In a double-blind, active-controlled study, 84 subjects with BPD I were randomly assigned to receive endoxifen (4 mg/day or 8 mg/day) or divalproex in a 2:1 ratio. Patients orally administered 4 mg/day or 8 mg/day endoxifen showed significant improvement in mania assessed by the Young Mania Rating Scale as early as 4 days. The effect remained significant throughout the 21-day period. At study end point, response rates were 44.44% and 64.29% at 4 mg/day and 8 mg/day of endoxifen treatment, respectively. Thus, endoxifen has been shown as a promising novel antimanic or mood stabilizing agent.

Study Highlights**WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?**

✓ PKC inhibitors are new compounds for the treatment of bipolar I disorder and mood-stabilizing agents.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ The study addressed the efficacy and safety of endoxifen at two doses in the treatment of patients with bipolar disorder I.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE?

✓ This prospective clinical trial demonstrated that endoxifen, a protein kinase C inhibitor, acts rapidly and demonstrated for the first time an antimanic activity in

Volume 9, Issue 5
October 2016
Pages 252-259

Figures References Related Information

Recommended

Endoxifen, a New Cornerstone of Breast Cancer Therapy: Demonstration of Safety, Tolerability, and Systemic Bioavailability in Healthy Human Subjects

A Ahmad, S Shahabuddin, S Sheikh, P Kale, M Krishnappa, R C Rane, I Ahmad

Clinical Pharmacology & Therapeutics

Increasing Tamoxifen Dose in Breast Cancer Patients Based on CYP2D6 Genotypes and Endoxifen Levels: Effect on Active Metabolite Isomers and the Antiestrogenic Activity Score

M F Barginear, M Jaremko, I Peter, C Yu, Y Kasai, M Kemeny, G Raptis, R J Desnick

Clinical Pharmacology & Therapeutics

Lithium in mania



patients with bipolar disorder I. Endoxifen was well tolerated by patients. Furthermore, the endoxifen amount required for the antimanic activity is 125–250-fold less than divalproex (active-control), a commonly used drug for the treatment of this disease.

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HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

✓ This is the first clinical study to elucidate the safety and antimanic effects of endoxifen in patients with bipolar I disorder. These findings on endoxifen deserve to be studied in a phase III trial.

The protein kinase C (PKC) is a family of serine/threonine kinases, which are known to play a vital role in cell signaling pathways. It regulates multiple neuronal processes implicated in mood regulation.^{1, 2} In current clinical practice, antidepressants and mood stabilizers have been shown to modulate the PKC pathway. Disrupted PKC activity has been found both in postmortem brains and platelet from patients with mood disorders. Accumulating evidence suggests an imbalance of the PKC signaling system in mood disorders. Thus, PKC may be a novel molecular target for the development of innovative medicine for bipolar disorder (BP). This is a chronic, debilitating illness that affects 0.4% to 4% of the US population.^{3, 4} The causes of BP are still unknown and no agent has been specifically developed on the basis of an understanding of the pathophysiology of the illness or mechanism of action for effective treatments. However, several drugs have been approved such as lithium, valproate, carbamazepine, and atypical antipsychotics for the treatment of acute bipolar mania.⁵ While these drugs have provided relief for many individuals with BP, significant issues with tolerability and efficacy still remain. The clinicians, for example, may find themselves in situations in which better-tolerated agents are less effective, and vice versa. Also, the adherence to the treatment is affected by adverse effects such as sedation and weight gain. Therefore, there is an urgent need to develop novel and more effective treatments for BP.

Two placebo-controlled, randomized trials of a PKC inhibitor drug, tamoxifen, were carried out independently.^{6, 7} These studies indicated that tamoxifen has strong antimanic properties both in men and women. Tamoxifen is extensively metabolized predominantly by the cytochrome P450s (CYP450) system to several primary and secondary metabolites including active metabolite endoxifen.⁸ We reported earlier the endoxifen (Figure 1) synthesis and its superior inhibitory PKC activity compared with tamoxifen. Endoxifen showed fourfold higher potency in inhibiting the PKC activity compared with tamoxifen.⁹ Endoxifen, being the active metabolite of tamoxifen, is not dependent on drug-metabolizing enzymes such as CYP450 and especially major polymorphic isozyme CYP2D6. In addition, the avoidance of CYP2D6-mediated drug metabolism represents an early Go / No Go decision criteria in central nervous system (CNS) drug discovery efforts because of its potential for variable patient safety and drug efficacy arising from genetic polymorphisms and its involvement in the metabolism of many existing drugs.

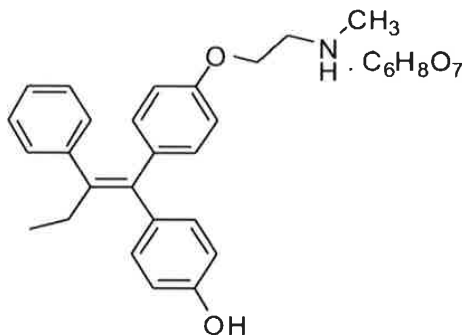


Figure 1

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Chemical structure of endoxifen.

To the best of our knowledge, this is the first report that describes the findings of a randomized, double-blind, active-controlled clinical trial to evaluate efficacy and safety of endoxifen in BPD I patients with current manic or mixed episode.

METHODS

Conduct of the clinical study

Written informed consent was obtained from all patients before enrollment. The clinical study was initiated as per the protocol after approval from the Independent Ethics Committee or Institutional Review Board. In addition, the study was conducted as per the International Conference on Harmonization Good Clinical Practice based on the basic principles of Good Laboratory Practice, Indian Council of Medical Research Guidelines for Biomedical Research on human subjects, and the Declaration of Helsinki (Seoul, 2008) on the rights of research participants. Safety assessments were based on adverse event (AE) reporting, laboratory testing, daily physical examination, recording of vital signs, and electrocardiograms.

Patients

Inclusion criteria: Male and female patients, 18 to 65 (both inclusive) years of age willing to give written informed consent along with at least one first-degree relative / legally acceptable representative (LAR), who were capable of understanding the purposes and risks of the trial and had given written informed consent, which included compliance with the study requirements and restrictions listed in the consent form, patients who were diagnosed of BPD I and having displayed an acute manic or mixed episode (with or without psychotic features) according to DSM-IV-TR as judged by the investigator. The patients were previously treated with at least one of the drugs, viz., lithium, valproate, carbamazepine, or an atypical (except for clozapine) or typical antipsychotic at some time during the course of their bipolar illness. Their last intake of the medication(s) for BPD I was within 2–7 days prior to randomization, depending on the individual drug's plasma half-life. The male patients of child-begetting potential and female patients of child-bearing potential, who were practicing adequate contraception, were enrolled in the study. Female patients were not pregnant or lactating and had a negative serum pregnancy test at the time of screening and negative urine pregnancy test at the time of randomization. The patients had a Young Mania Rating Scale (YMRS) total score of ≥ 20 and a score of ≥ 4 on the Clinical Global Impressions – Severity of Illness (CGI-S) Scale at the time of screening and at randomization (baseline).

Exclusion criteria: Newly diagnosed and not having any suitable treatment exposure in the past for their bipolar mood disorder; clinically significant suicidal or homicidal ideation; serious, unstable illnesses including hepatic, renal, gastroenterologic, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic, immunologic, or hematologic disease as per history and medical examination.

Methodology

This was a randomized, double-blind, double-dummy, active-controlled, two-arm, 3-week active treatment, two-stage parallel assignment, inpatient study. The study was coordinated by a Clinical Research Organization. This multisite study compared fixed-doses of endoxifen (4 mg or 8 mg) and extended release tablets of divalproex 1,000 mg for the treatment of BPD I. Before randomization to the 3-week double-blind treatment phase, the subjects underwent a screening and a washout period of 1 week after signing a written informed consent with at least one first-degree relative / LAR staying with the patient. The schema of this trial is shown in **Figure 2**.

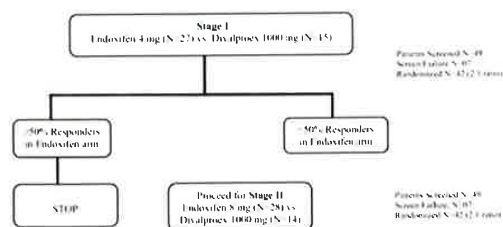


Figure 2

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Study design.

Patients entering the study were randomly assigned 2:1 (endoxifen:divalproex) in randomized and double-blinded fashion for 21 days. Endoxifen was given orally as enteric coated tablets at two fixed doses (4 mg/day or 8 mg/day) to enhance the bioavailability.

Blinding

The actual treatment given to individual patients was determined by a randomization schedule prepared at Lambda Therapeutic Research, India. The randomization schedule was generated using SAS v. 9.3 (Cary, NC) by an unblinded biostatistician before commencement of the study.

The pharmacy custodian verified the randomization schedule for correctness. The randomization schedule was kept under controlled access, which was handled only by the pharmacy custodian or designate, until the blind was broken. A control copy of the randomization schedule was provided as per the access level ensuring the blind. Study medication for each individual patient was prepackaged and prenumbered and provided to each participating site according to the randomization schedule. A designated pharmacy employee dispensed the study medication serially at the site.

The blind was to be broken only if knowledge of the treatment regimen assisted medical management of the patient in an acute emergency. The date, time, and reason for breaking the code had to be documented in the source documents and on the Case Report Form, and a serious adverse event was to be reported if the event met the serious criteria. On breaking the treatment randomization code in case of an emergency, the patient was to be withdrawn from the study.

Concomitant medications

All psychotropic medications except benzodiazepines (lorazepam/diazepam only) were discontinued at least 2 days before randomization. Benzodiazepines (lorazepam/diazepam only) (up to 5 mg/day, preferably in divided doses) were allowed as adjunctive medication as needed at the discretion of the investigator from 2 days prior to randomization but not beyond the first 10 days of investigational medicinal product dosing. Benzodiazepines were avoided within 12 h of scheduled mania ratings. The usage of two benzodiazepines was permitted to reduce undue excitement by using these adjuvants in an appropriate manner while avoiding efficacy or safety overlap with the endoxifen or divalproex. Several reports have been published about evaluation of mood-stabilizing drugs where concomitant intake of benzodiazepines was permitted during the study.¹⁰⁻¹²

Pharmacokinetic assessments

Predose PK samples were collected. The treatment was started by orally administering investigational medications from Day 0 onwards. Four mL blood for the Day 0 sample and 2 mL blood samples on Day 4, Day 7, Day 14, and Day 20 were collected from patients just before dosing the investigational medications at the clinic/hospital site. The last sample of 2 mL was collected on Day 49 when the patient visited the site for posttreatment safety follow-up. A total of six samples were collected per patient for PK assessment.

The blood samples were processed to separate plasma and blood cells. The plasma samples were then frozen at -20°C until use. Plasma samples of patients were analyzed using a validated LC-MS/MS method^{13, 14} for endoxifen at the bioanalytical facility of Lambda Therapeutic Research Ltd., Ahmedabad, India. The concentration data were tabulated using WinNonlin Professional Software v. 5.3 (Pharsight, Princeton, NJ).

The area under the curve (AUC) was estimated using Excel with the linear trapezoidal method. For a given time interval ($t_1 - t_2$), the AUC were calculated with the following equation:

$$\text{AUC} = \frac{1}{2} (C_1 + C_2) (t_2 - t_1)$$

Where C is the plasma concentration of endoxifen at a given time (t) of each patient. In this case, $C_1 = 0$, $t_1 = 0$. The dose-response relationship between mean YMRS score (change from baseline) and mean corresponding AUC at a certain time point was also analyzed using Excel and a linear regression that was illustrated in a semilogarithmic graph.

Efficacy and safety assessments

All psychiatrists participating in this double-blind trial at different sites were well trained and had experience in using Diagnostic & Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). All baseline scores were recorded by due administration of all defined scales. Efficacy and safety assessments were done based on evaluation parameters on Days 4, 7, 14, and 21 (end of treatment). Safety blood Clinical Global Impression of Improvement (CGI-I) was collected on Day 21 / discharge day from hospital. The primary end point was defined as the proportion of responders in each arm on Day 21 based on change in the Young Mania Rating Scale (YMRS) total score ($\geq 50\%$ decrease from baseline). Secondary end points were mean change from baseline to the end of treatment in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score, Clinical Global Impressions-Severity of Illness Scale (CGI-S) score, and Columbia-Suicide Severity Rating Scale (C-SSRS) score.

All statistical and safety analysis was performed using SAS v. 9.3 (SAS Institute, Cary, NC).

RESULTS

Patient characteristics and study design

A total of 84 patients who met the requirements for the study and provided informed written consent for participation were enrolled in this trial. The mean $\pm$ SD for age of these 84 patients was 36.8 ± 11.9 years. The study was conducted at various hospitals in India with a racial makeup of 100% Asian.

The study was conducted in two stages (Figure 2). A total of 42 patients were randomized in each stage of the study across two arms in a 2:1 ratio. In stage I, 27 (instead of 28) and 15 (instead of 14) patients were randomized to endoxifen 4 mg and divalproex 1,000 mg arms, respectively. This happened due to site-specific randomization and the double-blind, double-dummy design of the study. In stage II, 28 patients were randomized to endoxifen 8 mg arm and 14 patients to divalproex 1,000 mg arm. A total of 84 patients were dosed in the trial (42 patients in each stage). Of these 84 patients, 6 patients were withdrawn/discontinued from the study. Two patients were withdrawn from the trial due to adverse event. Another two patients withdrew their consent from the trial and one patient lost to follow-up.

Thus, 78 patients completed the clinical phase of the study at five sites. The plasma samples of all 84 patients were collected.

Efficacy

The mean change in the YMRS total score from baseline was used to evaluate the effectiveness of antimanic medications. Using the analysis of variance (ANOVA) model of SAS, the total YMRS score at baseline and end of trial assessment was found to be statistically significant ($P < 0.0001$) across the sites. The mean change in YMRS score from baseline was found to be -12.65 , -16.21 , and -16.38 in endoxifen 4 mg, 8 mg, and divalproex 1,000 mg arm, respectively (Figure 3a). This percent change from baseline to each subsequent assessment in total YMRS score is shown in Figure 3b. The mean change in the intent-to-treat (ITT) population was not statistically significant among different groups.

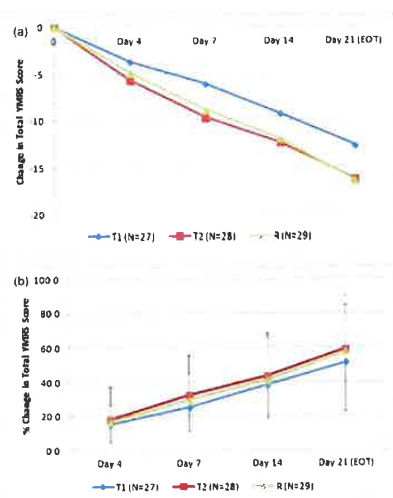


Figure 3

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(a) Mean change in baseline from total YMRS score. (b) Percent change from the baseline to each subsequent assessment in the total YMRS score. T1 = endoxifen 4 mg/day; T2 = endoxifen 8 mg/day; R = divalproex 1,000 mg/day.

The percent change in the YMRS total score from baseline to end of the treatment was 54.68% and 55.36% in the endoxifen 4 mg and divalproex arm, respectively, in the per protocol (PP) data analysis in stage I. In stage II, the percent change was 58.98% and 65.06% in the endoxifen 8 mg and divalproex arm, respectively. The proportion of responders based on YMRS total score for endoxifen 4 mg/day (stage I), endoxifen 8 mg/day (stage II), and divalproex 1,000 mg/day (stage I + stage II) data are presented in Table 1. Statistically, the differences among groups were not significant. The response rate with the use of lithium,

valproate, and atypical antipsychotics such as olanzapine, risperidone, and paliperidone in White/Black/Asian was found to vary from 30–70%, which is comparable to this study.¹⁵⁻¹⁹

Table 1. Proportion of responders based on YMRS Score (ITT set)

	Endoxifen 4 mg/day (N = 27) n (%)	Endoxifen 8 mg/day (N = 28) n (%)	Divalproex R ^c 1000 mg/day (N = 29) n (%)
Responders ^a	12 (44.44%)	18 (64.29%)	21 (72.41%)
Nonresponders ^b	15 (55.56%)	10 (35.71%)	8 (27.59%)

^a Responders: ≥50% improvement for YMRS scores.

^b Nonresponders: <50% improvement for YMRS score.

^c R represents the combined data of stage I and stage II for divalproex used as reference.

Since a switch to depression remains a concern in all treatments of bipolar mania, depressive symptoms were assessed with the MADRS score throughout the trial. The result demonstrated the effectiveness of endoxifen 4 mg and 8 mg in alleviating depressive symptoms of mixed episode of BPD similar to that of divalproex.²⁰⁻²²

The CGI-S score at baseline was comparable in two arms of stage I and II, reflecting that most patients had marked or moderate manic symptoms. At the end of the 3-week study treatment, the CGI-S scores of most patients in all arms showed reductions indicative of no illness to mild illness states. Similar results were also observed in the CGI-I score in all arms. In the CGI-I, the score of a majority of the patients shifted to “very much improved” and “much improved” categories in all arms. The CGI-efficacy index is the scale that evaluates combined safety and efficacy of the medication. At the end of 3 weeks of treatment, this index was similar among the endoxifen 4 mg or 8 mg and divalproex arm. Similar results have been obtained with the use of other antimanic medications.^{6, 7, 23-25}

It is concluded that endoxifen at 8 mg appears to be more efficacious than endoxifen 4 mg and as effective as divalproex sodium extended release 1,000 mg in the treatment of BPD I with concurrent manic or mixed episode.

Safety and tolerability

The safety analysis included all 84 patients who received at least one dose of the study medication. A total of 63 adverse events (AEs) were reported by 27 patients during the conduct of this study. Out of 63, 59 were mild, 2 were moderate, and 2 were severe in intensity. In all, 33 AEs were reported by 41.38% (n = 12) of 29 patients in the divalproex arm and 19 AEs were reported by 29.63% (n = 8) of 27 patients in the endoxifen 4 mg arm and 11 AEs were reported by 25.00% (n = 07) of 28 patients in the endoxifen 8 mg arm. There were two patients who left the study in the 4 mg/day group due to adverse effect, three patients withdrew consent, and one patient was lost to follow-up. No patients left the study in the 8 mg/day endoxifen or in the divalproex arm. There were no deaths, other significant AEs, or serious AEs reported during the conduct of the study. Overall, endoxifen was well tolerated.

The most common AEs reported in the trial were psychiatric in nature. Insomnia and nausea were the most common AEs in the divalproex arm (**Table 2**). Headache was reported in two patients at endoxifen 4 mg, three patients at endoxifen 8 mg, and three patients in the divalproex 1,000 mg arm. Gastrointestinal disorders like dyspepsia, nausea, and vomiting were found in four, one, and seven patients in the endoxifen 4 mg, endoxifen 8 mg, and divalproex arm, respectively. Only two AEs were found to be severe in the 4 mg endoxifen group and one AE was moderate in the divalproex group; all other AEs were mild in nature. The two severe AEs observed in the 4 mg endoxifen group were related to delusions in patients. Based on the above results, it is concluded that endoxifen 4 mg and 8 mg was well tolerated and safe as compared with divalproex.

Table 2. Incidence of treatment related adverse events in BPD I patients

Adverse event	Endoxifen, 4 mg (N = 27)		Endoxifen, 8 mg (N = 28)		Divalproex, 1 gm (N = 28)	
	N	%	N	%	N	%
Patients with at least one AE	8	29.63	7	25	12	41.38
Nausea	1	3.7	1	3.57	5	17.24

Headache	2	7.4	3	10.71	3	10.34
Insomnia	1	3.7	2	7.14	5	17.24

Pharmacokinetics and pharmacokinetic-pharmacodynamic (PK-PD) relationship of endoxifen

The endoxifen plasma trough level concentration–time profile is shown in **Figure 4a** for both the 4 mg and 8 mg doses. The mean trough concentration (C_{trough}) of endoxifen (4 mg/day) for Day 14 and Day 20 were 28 ng/mL and 29 ng/mL, respectively. Similarly, the mean C_{trough} of endoxifen (8 mg/day) for Day 14 and Day 20 were found to be 58 ng/mL and 59 ng/mL, respectively. This showed that there is no significant difference when average C_{trough} concentrations of endoxifen were compared for Day 14 and Day 20, indicating that the steady-state of endoxifen was achieved within 14 days of endoxifen administration. The mean exposure (AUC, day.ng/mL) values on Day 14 ($AUC_{0-14\text{ days}}$) and Day 20 ($AUC_{0-20\text{ days}}$) for endoxifen at the 4 mg/day dose were 203.01 and 282.82, respectively, whereas for endoxifen at 8 mg/day doses were 399.58 and 586.82, respectively. This observation demonstrates that the doubling of dose from 4 mg to 8 mg once daily results in ~2-fold increase in plasma AUC. We have shown in our earlier single-dose study¹³ that AUC and maximum plasma concentration (C_{max}) for endoxifen increased in proportion to the dose from 0.5–4 mg. The mean terminal elimination half-life ($t_{1/2}$) of endoxifen after a single dose of 4 mg was 52.05 h. Additionally, we also showed in a multiple-dose study that at steady-state endoxifen displays dose-proportional PK with respect to C_{max} and AUC to the dose ranging from 2–8 mg. The data obtained in the current study reflect a similar profile.

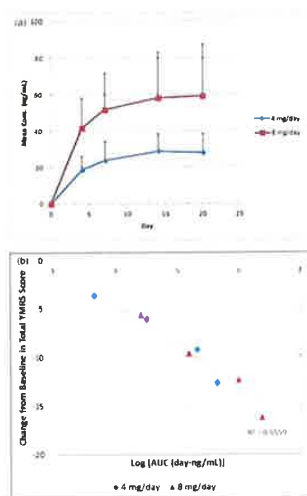


Figure 4 [Open in figure viewer](#) [PowerPoint](#)

(a) Plasma concentration profile of endoxifen at two doses of 4 mg/day and 8 mg/day. (b) Pharmacokinetic–pharmacodynamic relationship. AUC values were calculated from plasma concentration–time curve of endoxifen. Each AUC value represents the average of those from 24 (4 mg/day group) or 28 (8 mg/day group) patients.

In order to investigate a potential relationship between exposure levels of endoxifen and its antimanic effect, an exploratory exposure–response analysis for endoxifen was performed using data from the exposure (AUC) and PD end point of antimanic activity (YMRS total score) data. Such exposure–response analysis is increasingly recognized as necessary to optimize the benefits of small drug molecules such as endoxifen for patients. As shown in **Figure 4b**, the antimanic effect (response) of endoxifen monotherapy is manifested as the exposure is increased. Regression analysis of YMRS total score and AUC indicates that the relationship was linear, with $R^2 = 0.9559$.

DISCUSSION

This is the first controlled clinical trial that demonstrates that endoxifen, when used alone, significantly ($P < 0.0001$) reduces the manic symptoms associated with BPD I. Endoxifen, at two fixed doses, produced significantly greater improvements on the Young Mania Rating

Scale at almost every treatment evaluation. The evidence for efficacy and safety of endoxifen based on the controlled data observed in this trial provide an alternate treatment option to the physician and patients. The efficacy of endoxifen observed in this trial was not significantly different from divalproex, a "the first-line" pharmacological treatment for patients with mania. The duration of this trial (21 days) may be insufficient to adequately make clinical decisions regarding the efficacy and safety of long-term endoxifen treatment in patients with BPD I. Particularly, the effects of endoxifen on weight gain and metabolic parameters should be interpreted with caution.

As shown in **Table 3**, the magnitude of the endoxifen effect at 4 mg/day or 8 mg/day compares favorably with the magnitude of effect shown on the YMR5 in recently conducted 3-week monotherapy trials of BPD I with tamoxifen, aripiprazole, and olanzapine.^{6, 7, 22-25} Similar to other BPD I studies, a 3-week study duration was sufficient to assess endoxifen efficacy in the treatment of BPD I. Due to its PKC inhibitory as well as the antiestrogenic activity of endoxifen, the maximal utilization of this drug may be restricted. However, longer studies are needed to determine the efficacy and tolerability of endoxifen. In conclusion, orally administered endoxifen at 4 mg/day or 8 mg/day in this phase II clinical trial was well tolerated and showed significant improvement in manic or mixed episodes patients.

Table 3. Monotherapy trials of drugs for the treatment of BP

Drug and study	Trial duration (weeks)	Baseline Young Mania Rating Scale score	Change from baseline	Onset of action (day)
Tamoxifen				
Zarrate <i>et al.</i> ⁶	3	30	-18.3	4
Yildiz <i>et al.</i> ⁷	3	38	-16.6	4
Aripiprazole				
Sach <i>et al.</i> ²²	3	29	-12.5	4
Keck <i>et al.</i> ²³	3	28	-8.2	4
Olanzapine				
Tohen <i>et al.</i> ²⁴	3	28	-10.3	7
Tohen <i>et al.</i> ²⁵	4	29	-14.8	7
Endoxifen				
4 mg/ day	3	24	-12.65	4
8 mg/day	3	27	-16.22	4
Valproate				
Divalproex (1000 mg/day)	3	28	-16.38	4

Author Contributions

A.A., S.S., and I.A. wrote the article; A.A., S.S., and I.A. designed the research; T.S., M.S.R., B.S.V.P., K.K.V., B.B.C., M.P., and P.K. performed the research; A.A., S.S., I.A., M.P., P.K., R.V.S., H.B., and R.P. analyzed the data.

Conflict of Interest/Disclosure

The authors declare no conflicts of interest.

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ARTICLE

Endoxifen, a New Treatment Option for Mania: A Double-Blind, Active-Controlled Trial Demonstrates the Antimanic Efficacy of Endoxifen

A Ahmad¹, S Sheikh¹, T Shah², MS Reddy³, BSV Prasad⁴, KK Verma⁵, BB Chandrakant⁶, M Paithankar⁷, P Kale⁸, RV Solanki⁸, R Patel⁸, H Barkate⁷ and I Ahmad^{1,*}

The protein kinase C (PKC) signaling system plays a role in mood disorders and PKC inhibitors such as endoxifen may be an innovative medicine for bipolar disorder (BP) patients. In this study we show for the first time the antimanic properties of endoxifen in patients with bipolar I disorder (BPD I) with current manic or mixed episode. In a double-blind, active-controlled study, 84 subjects with BPD I were randomly assigned to receive endoxifen (4 mg/day or 8 mg/day) or divalproex in a 2:1 ratio. Patients orally administered 4 mg/day or 8 mg/day endoxifen showed significant improvement in mania assessed by the Young Mania Rating Scale as early as 4 days. The effect remained significant throughout the 21-day period. At study end point, response rates were 44.44% and 64.29% at 4 mg/day and 8 mg/day of endoxifen treatment, respectively. Thus, endoxifen has been shown as a promising novel antimanic or mood stabilizing agent.

Clin Transl Sci (2016) 9, 252–259; doi:10.1111/cts.12407; published online on 27 June 2016.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

PKC inhibitors are new compounds for the treatment of bipolar I disorder and mood-stabilizing agents.

WHAT QUESTION DID THIS STUDY ADDRESS?

The study addressed the efficacy and safety of endoxifen at two doses in the treatment of patients with bipolar disorder I.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE?

This prospective clinical trial demonstrated that endoxifen, a protein kinase C inhibitor, acts rapidly and demonstrated for the first time an antimanic activity in patients with

bipolar disorder I. Endoxifen was well tolerated by patients. Furthermore, the endoxifen amount required for the antimanic activity is 125–250-fold less than divalproex (active-control), a commonly used drug for the treatment of this disease.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

This is the first clinical study to elucidate the safety and antimanic effects of endoxifen in patients with bipolar I disorder. These findings on endoxifen deserve to be studied in a phase III trial.

The protein kinase C (PKC) is a family of serine/threonine kinases, which are known to play a vital role in cell signaling pathways. It regulates multiple neuronal processes implicated in mood regulation.^{1,2} In current clinical practice, antidepressants and mood stabilizers have been shown to modulate the PKC pathway. Disrupted PKC activity has been found both in postmortem brains and platelet from patients with mood disorders. Accumulating evidence suggests an imbalance of the PKC signaling system in mood disorders. Thus, PKC may be a novel molecular target for the development of innovative medicine for bipolar disorder (BP). This is a chronic, debilitating illness that affects 0.4% to 4% of the US population.^{3,4} The causes of BP are still unknown and no agent has been specifically developed on the basis of an understanding of the pathophysiology of the illness or

mechanism of action for effective treatments. However, several drugs have been approved such as lithium, valproate, carbamazepine, and atypical antipsychotics for the treatment of acute bipolar mania.⁵ While these drugs have provided relief for many individuals with BP, significant issues with tolerability and efficacy still remain. The clinicians, for example, may find themselves in situations in which better-tolerated agents are less effective, and vice versa. Also, the adherence to the treatment is affected by adverse effects such as sedation and weight gain. Therefore, there is an urgent need to develop novel and more effective treatments for BP.

Two placebo-controlled, randomized trials of a PKC inhibitor drug, tamoxifen, were carried out independently.^{6,7} These studies indicated that tamoxifen has strong

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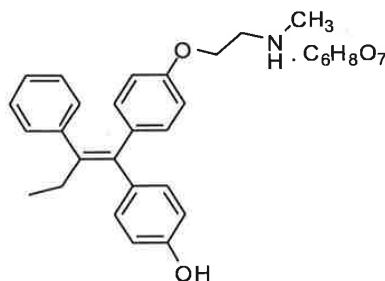


Figure 1 Chemical structure of endoxifen.

antimanic properties both in men and women. Tamoxifen is extensively metabolized predominantly by the cytochrome P450s (CYP450) system to several primary and secondary metabolites including active metabolite endoxifen.⁸ We reported earlier the endoxifen (**Figure 1**) synthesis and its superior inhibitory PKC activity compared with tamoxifen. Endoxifen showed fourfold higher potency in inhibiting the PKC activity compared with tamoxifen.⁹ Endoxifen, being the active metabolite of tamoxifen, is not dependent on drug-metabolizing enzymes such as CYP450 and especially major polymorphic isozyme CYP2D6. In addition, the avoidance of CYP2D6-mediated drug metabolism represents an early Go / No Go decision criteria in central nervous system (CNS) drug discovery efforts because of its potential for variable patient safety and drug efficacy arising from genetic polymorphisms and its involvement in the metabolism of many existing drugs.

To the best of our knowledge, this is the first report that describes the findings of a randomized, double-blind, active-controlled clinical trial to evaluate efficacy and safety of endoxifen in BPD I patients with current manic or mixed episode.

METHODS

Conduct of the clinical study

Written informed consent was obtained from all patients before enrollment. The clinical study was initiated as per the protocol after approval from the Independent Ethics Committee or Institutional Review Board. In addition, the study was conducted as per the International Conference on Harmonization Good Clinical Practice based on the basic principles of Good Laboratory Practice, Indian Council of Medical Research Guidelines for Biomedical Research on human subjects, and the Declaration of Helsinki (Seoul, 2008) on the rights of research participants. Safety assessments were based on adverse event (AE) reporting, laboratory testing, daily physical examination, recording of vital signs, and electrocardiograms.

Patients

Inclusion criteria: Male and female patients, 18 to 65 (both inclusive) years of age willing to give written informed consent along with at least one first-degree relative / legally acceptable representative (LAR), who were capable of understanding the purposes and risks of the trial and had

given written informed consent, which included compliance with the study requirements and restrictions listed in the consent form, patients who were diagnosed of BPD I and having displayed an acute manic or mixed episode (with or without psychotic features) according to DSM-IV-TR as judged by the investigator. The patients were previously treated with at least one of the drugs, viz., lithium, valproate, carbamazepine, or an atypical (except for clozapine) or typical antipsychotic at some time during the course of their bipolar illness. Their last intake of the medication(s) for BPD I was within 2–7 days prior to randomization, depending on the individual drug's plasma half-life. The male patients of child-begetting potential and female patients of child-bearing potential, who were practicing adequate contraception, were enrolled in the study. Female patients were not pregnant or lactating and had a negative serum pregnancy test at the time of screening and negative urine pregnancy test at the time of randomization. The patients had a Young Mania Rating Scale (YMRS) total score of ≥ 20 and a score of ≥ 4 on the Clinical Global Impressions – Severity of Illness (CGI-S) Scale at the time of screening and at randomization (baseline).

Exclusion criteria: Newly diagnosed and not having any suitable treatment exposure in the past for their bipolar mood disorder; clinically significant suicidal or homicidal ideation; serious, unstable illnesses including hepatic, renal, gastroenterologic, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic, immunologic, or hematologic disease as per history and medical examination.

Methodology

This was a randomized, double-blind, double-dummy, active-controlled, two-arm, 3-week active treatment, two-stage parallel assignment, inpatient study. The study was coordinated by a Clinical Research Organization. This multisite study compared fixed-doses of endoxifen (4 mg or 8 mg) and extended release tablets of divalproex 1,000 mg for the treatment of BPD I. Before randomization to the 3-week double-blind treatment phase, the subjects underwent a screening and a washout period of 1 week after signing a written informed consent with at least one first-degree relative / LAR staying with the patient. The schema of this trial is shown in **Figure 2**.

Patients entering the study were randomly assigned 2:1 (endoxifen:divalproex) in randomized and double-blinded fashion for 21 days. Endoxifen was given orally as enteric coated tablets at two fixed doses (4 mg/day or 8 mg/day) to enhance the bioavailability.

Blinding

The actual treatment given to individual patients was determined by a randomization schedule prepared at Lambda Therapeutic Research, India. The randomization schedule was generated using SAS v. 9.3 (Cary, NC) by an unblinded biostatistician before commencement of the study.

The pharmacy custodian verified the randomization schedule for correctness. The randomization schedule was kept under controlled access, which was handled only by the pharmacy custodian or designate, until the blind was broken. A control copy of the randomization schedule was

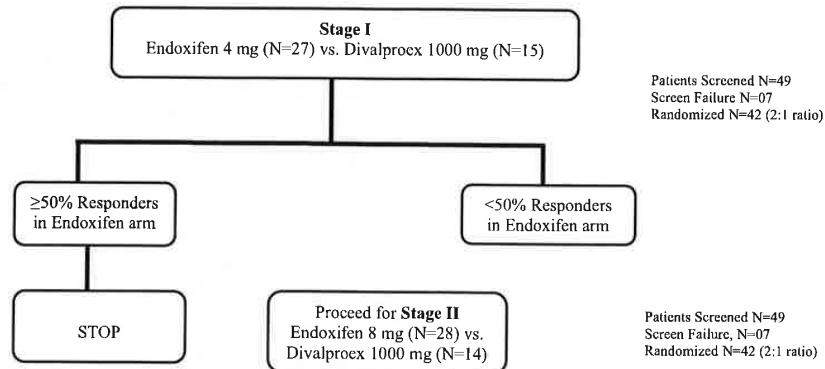


Figure 2 Study design.

provided as per the access level ensuring the blind. Study medication for each individual patient was prepackaged and prenumbered and provided to each participating site according to the randomization schedule. A designated pharmacy employee dispensed the study medication serially at the site.

The blind was to be broken only if knowledge of the treatment regimen assisted medical management of the patient in an acute emergency. The date, time, and reason for breaking the code had to be documented in the source documents and on the Case Report Form, and a serious adverse event was to be reported if the event met the serious criteria. On breaking the treatment randomization code in case of an emergency, the patient was to be withdrawn from the study.

Concomitant medications

All psychotropic medications except benzodiazepines (lorazepam/diazepam only) were discontinued at least 2 days before randomization. Benzodiazepines (lorazepam/diazepam only) (up to 5 mg/day, preferably in divided doses) were allowed as adjunctive medication as needed at the discretion of the investigator from 2 days prior to randomization but not beyond the first 10 days of investigational medicinal product dosing. Benzodiazepines were avoided within 12 h of scheduled mania ratings. The usage of two benzodiazepines was permitted to reduce undue excitement by using these adjuvants in an appropriate manner while avoiding efficacy or safety overlap with the endoxifen or divalproex. Several reports have been published about evaluation of mood-stabilizing drugs where concomitant intake of benzodiazepines was permitted during the study.^{10–12}

Pharmacokinetic assessments

Predose PK samples were collected. The treatment was started by orally administering investigational medications from Day 0 onwards. Four mL blood for the Day 0 sample and 2 mL blood samples on Day 4, Day 7, Day 14, and Day 20 were collected from patients just before dosing the investigational medications at the clinic/hospital site. The last sample of 2 mL was collected on Day 49 when the patient visited the site for posttreatment safety follow-up. A total of six samples were collected per patient for PK assessment.

The blood samples were processed to separate plasma and blood cells. The plasma samples were then frozen at -20°C until use. Plasma samples of patients were analyzed using a validated LC-MS/MS method^{13,14} for endoxifen at the bioanalytical facility of Lambda Therapeutic Research Ltd., Ahmedabad, India. The concentration data were tabulated using WinNonlin Professional Software v. 5.3 (Pharsight, Princeton, NJ).

The area under the curve (AUC) was estimated using Excel with the linear trapezoidal method. For a given time interval ($t_1 - t_2$), the AUC were calculated with the following equation:

$$\text{AUC} = \frac{1}{2} (C_1 + C_2) (t_2 - t_1)$$

Where C is the plasma concentration of endoxifen at a given time (t) of each patient. In this case, $C_1 = 0$, $t_1 = 0$. The dose-response relationship between mean YMRS score (change from baseline) and mean corresponding AUC at a certain time point was also analyzed using Excel and a linear regression that was illustrated in a semilogarithmic graph.

Efficacy and safety assessments

All psychiatrists participating in this double-blind trial at different sites were well trained and had experience in using Diagnostic & Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). All baseline scores were recorded by due administration of all defined scales. Efficacy and safety assessments were done based on evaluation parameters on Days 4, 7, 14, and 21 (end of treatment). Safety blood Clinical Global Impression of Improvement (CGI-I) was collected on Day 21 / discharge day from hospital. The primary end point was defined as the proportion of responders in each arm on Day 21 based on change in the Young Mania Rating Scale (YMRS) total score ($\geq 50\%$ decrease from baseline). Secondary end points were mean change from baseline to the end of treatment in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score, Clinical Global Impressions-Severity of Illness Scale (CGI-S) score, and Columbia-Suicide Severity Rating Scale (C-SSRS) score.

All statistical and safety analysis was performed using SAS v. 9.3 (SAS Institute, Cary, NC).

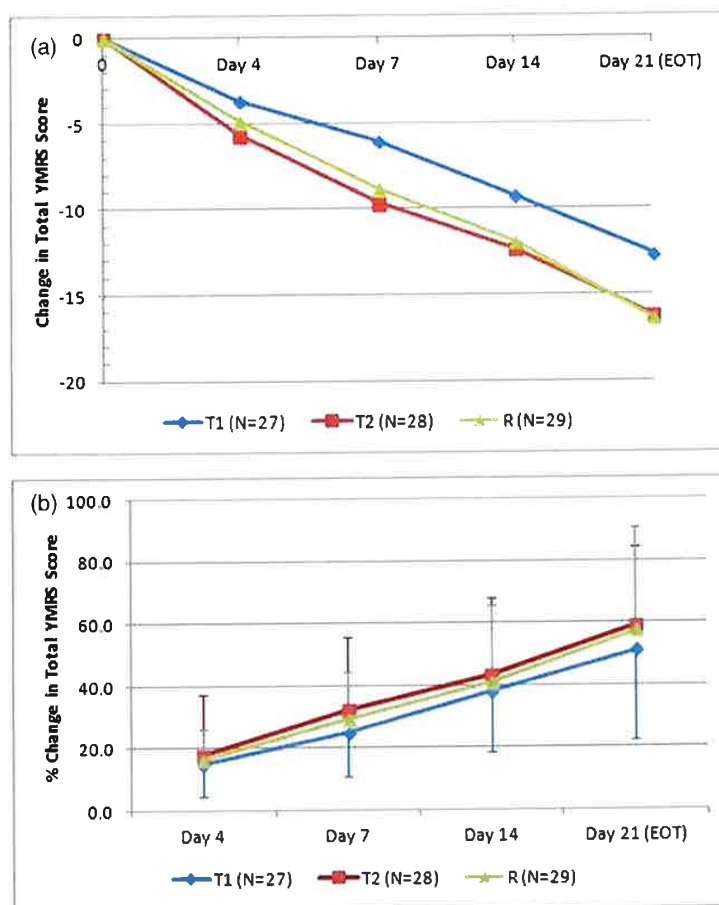


Figure 3 (a) Mean change in baseline from total YMRS score. (b) Percent change from the baseline to each subsequent assessment in the total YMRS score. T1 = endoxifen 4 mg/day; T2 = endoxifen 8 mg/day; R = divalproex 1,000 mg/day.

RESULTS

Patient characteristics and study design

A total of 84 patients who met the requirements for the study and provided informed written consent for participation were enrolled in this trial. The mean $\pm$ SD for age of these 84 patients was 36.8 ± 11.9 years. The study was conducted at various hospitals in India with a racial makeup of 100% Asian.

The study was conducted in two stages (Figure 2). A total of 42 patients were randomized in each stage of the study across two arms in a 2:1 ratio. In stage I, 27 (instead of 28) and 15 (instead of 14) patients were randomized to endoxifen 4 mg and divalproex 1,000 mg arms, respectively. This happened due to site-specific randomization and the double-blind, double-dummy design of the study. In stage II, 28 patients were randomized to endoxifen 8 mg arm and 14 patients to divalproex 1,000 mg arm. A total of 84 patients were dosed in the trial (42 patients in each stage). Of these 84 patients, 6 patients were withdrawn/discontinued from

the study. Two patients were withdrawn from the trial due to adverse event. Another two patients withdrew their consent from the trial and one patient lost to follow-up.

Thus, 78 patients completed the clinical phase of the study at five sites. The plasma samples of all 84 patients were collected.

Efficacy

The mean change in the YMRS total score from baseline was used to evaluate the effectiveness of antimanic medications. Using the analysis of variance (ANOVA) model of SAS, the total YMRS score at baseline and end of trial assessment was found to be statistically significant ($P < 0.0001$) across the sites. The mean change in YMRS score from baseline was found to be -12.65 , -16.21 , and -16.38 in endoxifen 4 mg, 8 mg, and divalproex 1,000 mg arm, respectively (Figure 3a). This percent change from baseline to each subsequent assessment in total YMRS score is shown in Figure 3b. The mean change in the intent-to-treat (ITT) population was not statistically significant among different groups.

Table 1 Proportion of responders based on YMRS Score (ITT set)

	Endoxifen 4 mg/day (N = 27) n (%)	Endoxifen 8 mg/day (N = 28) n (%)	Divalproex R ^c 1000 mg/day (N = 29) n (%)
Responders ^a	12 (44.44%)	18 (64.29%)	21 (72.41%)
Nonresponders ^b	15 (55.56%)	10 (35.71%)	8 (27.59%)

^aResponders: ≥50% improvement for YMRS scores.

^bNonresponders: <50% improvement for YMRS score.

^cR represents the combined data of stage I and stage II for divalproex used as reference.

The percent change in the YMRS total score from baseline to end of the treatment was 54.68% and 55.36% in the endoxifen 4 mg and divalproex arm, respectively, in the per protocol (PP) data analysis in stage I. In stage II, the percent change was 58.98% and 65.06% in the endoxifen 8 mg and divalproex arm, respectively. The proportion of responders based on YMRS total score for endoxifen 4 mg/day (stage I), endoxifen 8 mg/day (stage II), and divalproex 1,000 mg/day (stage I + stage II) data are presented in **Table 1**. Statistically, the differences among groups were not significant. The response rate with the use of lithium, valproate, and atypical antipsychotics such as olanzapine, risperidone, and paliperidone in White/Black/Asian was found to vary from 30–70%, which is comparable to this study.^{15–19}

Since a switch to depression remains a concern in all treatments of bipolar mania, depressive symptoms were assessed with the MADRS score throughout the trial. The result demonstrated the effectiveness of endoxifen 4 mg and 8 mg in alleviating depressive symptoms of mixed episode of BPD similar to that of divalproex.^{20–22}

The CGI-S score at baseline was comparable in two arms of stage I and II, reflecting that most patients had marked or moderate manic symptoms. At the end of the 3-week study treatment, the CGI-S scores of most patients in all arms showed reductions indicative of no illness to mild illness states. Similar results were also observed in the CGI-I score in all arms. In the CGI-I, the score of a majority of the patients shifted to “very much improved” and “much improved” categories in all arms. The CGI-efficacy index is the scale that evaluates combined safety and efficacy of the medication. At the end of 3 weeks of treatment, this index was similar among the endoxifen 4 mg or 8 mg and divalproex arm. Similar results have been obtained with the use of other antimanic medications.^{6,7,23–25}

It is concluded that endoxifen at 8 mg appears to be more efficacious than endoxifen 4 mg and as effective as divalproex sodium extended release 1,000 mg in the treatment of BPD I with concurrent manic or mixed episode.

Safety and tolerability

The safety analysis included all 84 patients who received at least one dose of the study medication. A total of 63 adverse events (AEs) were reported by 27 patients during the conduct of this study. Out of 63, 59 were mild, 2 were moderate, and 2 were severe in intensity. In all, 33 AEs were reported by 41.38% ($n = 12$) of 29 patients in the divalproex arm and 19 AEs were reported by 29.63% ($n = 8$) of 27 patients in the endoxifen 4 mg arm and 11 AEs were reported by 25.00% ($n = 07$) of 28 patients in the endoxifen 8 mg arm. There were two patients who left the study in the 4 mg/day group due to adverse effect, three patients withdrew consent, and one patient was lost to follow-up. No patients left the study in the 8 mg/day endoxifen or in the divalproex arm. There were no deaths, other significant AEs, or serious AEs reported during the conduct of the study. Overall, endoxifen was well tolerated.

The most common AEs reported in the trial were psychiatric in nature. Insomnia and nausea were the most common AEs in the divalproex arm (**Table 2**). Headache was reported in two patients at endoxifen 4 mg, three patients at endoxifen 8 mg, and three patients in the divalproex 1,000 mg arm. Gastrointestinal disorders like dyspepsia, nausea, and vomiting were found in four, one, and seven patients in the endoxifen 4 mg, endoxifen 8 mg, and divalproex arm, respectively. Only two AEs were found to be severe in the 4 mg endoxifen group and one AE was moderate in the divalproex group; all other AEs were mild in nature. The two severe AEs observed in the 4 mg endoxifen group were related to delusions in patients. Based on the above results, it is concluded that endoxifen 4 mg and 8 mg was well tolerated and safe as compared with divalproex.

Pharmacokinetics and pharmacokinetic-pharmacodynamic (PK-PD) relationship of endoxifen

The endoxifen plasma trough level concentration–time profile is shown in **Figure 4a** for both the 4 mg and 8 mg doses. The mean trough concentration (C_{trough}) of endoxifen (4 mg/day) for Day 14 and Day 20 were 28 ng/mL and 29 ng/mL, respectively. Similarly, the mean C_{trough} of endoxifen (8 mg/day) for Day 14 and Day 20 were found to be 58 ng/mL and 59 ng/mL, respectively. This showed that there is no significant difference when average C_{trough} concentrations of endoxifen were compared for Day 14 and Day 20, indicating that the steady-state of endoxifen was achieved within 14 days of endoxifen administration. The mean exposure (AUC, day.ng/mL) values on Day 14 (AUC_{0–14 days}) and Day 20 (AUC_{0–20 days}) for endoxifen at the 4 mg/day dose were 203.01 and 282.82, respectively, whereas for endoxifen at 8 mg/day doses were 399.58 and 586.82, respectively. This observation demonstrates that

Table 2 Incidence of treatment related adverse events in BPD I patients

Adverse event	Endoxifen, 4 mg (N = 27)		Endoxifen, 8 mg (N = 28)		Divalproex, 1 gm (N = 28)	
	N	%	N	%	N	%
Patients with at least one AE	8	29.63	7	25	12	41.38
Nausea	1	3.7	1	3.57	5	17.24
Headache	2	7.4	3	10.71	3	10.34
Insomnia	1	3.7	2	7.14	5	17.24

the doubling of dose from 4 mg to 8 mg once daily results in ~2-fold increase in plasma AUC. We have shown in our earlier single-dose study¹³ that AUC and maximum plasma concentration (C_{max}) for endoxifen increased in proportion to the dose from 0.5–4 mg. The mean terminal elimination half-life ($t_{1/2}$) of endoxifen after a single dose of 4 mg was 52.05 h. Additionally, we also showed in a multiple-dose study that at

steady-state rate endoxifen displays dose-proportional PK with respect to C_{max} and AUC to the dose ranging from 2–8 mg. The data obtained in the current study reflect a similar profile.

In order to investigate a potential relationship between exposure levels of endoxifen and its antimanic effect, an exploratory exposure–response analysis for endoxifen was

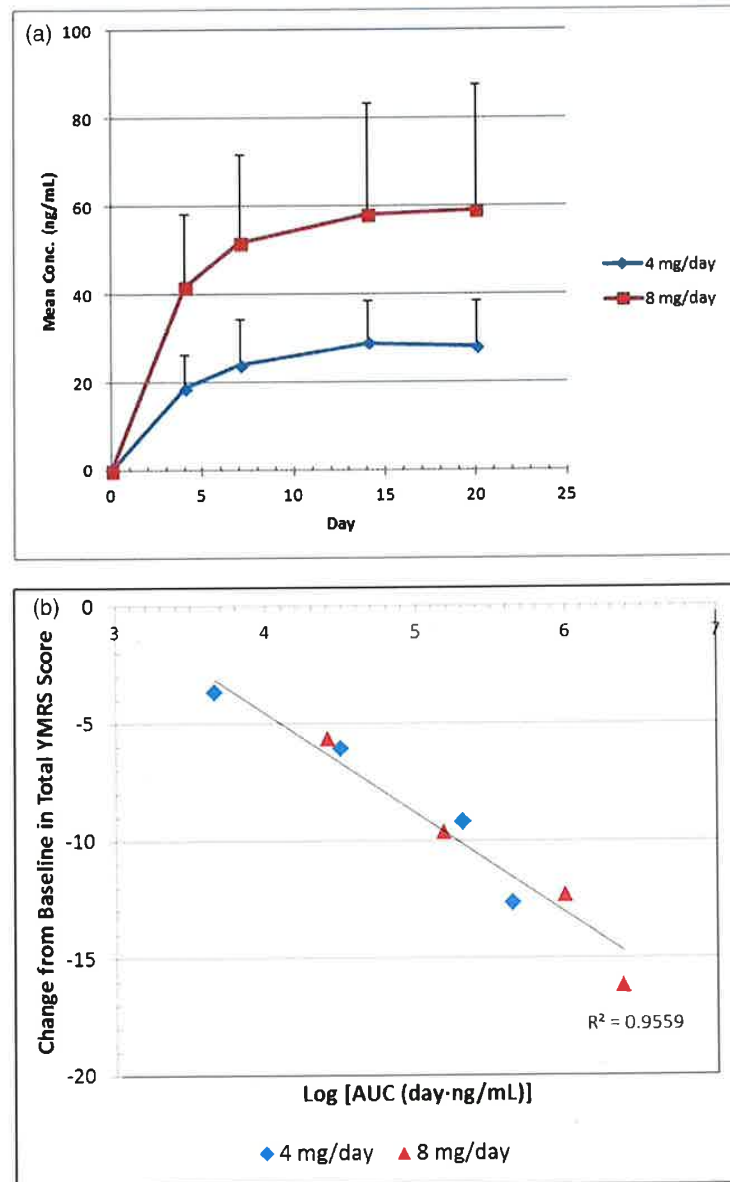


Figure 4 (a) Plasma concentration profile of endoxifen at two doses of 4 mg/day and 8 mg/day. (b) Pharmacokinetic–pharmacodynamic relationship. AUC values were calculated from plasma concentration–time curve of endoxifen. Each AUC value represents the average of those from 24 (4 mg/day group) or 28 (8 mg/day group) patients.

Table 3 Monotherapy trials of drugs for the treatment of BP

Drug and study	Trial duration (weeks)	Baseline Young Mania Rating Scale score	Change from baseline	Onset of action (day)
Tamoxifen				
Zarrate et al. ⁶	3	30	-18.3	4
Yildiz et al. ⁷	3	38	-16.6	4
Aripiprazole				
Sach et al. ²²	3	29	-12.5	4
Keck et al. ²³	3	28	-8.2	4
Olanzapine				
Tohen et al. ²⁴	3	28	-10.3	7
Tohen et al. ²⁵	4	29	-14.8	7
Endoxifen				
4 mg/day	3	24	-12.65	4
8 mg/day	3	27	-16.22	4
Valproate				
Divalproex (1000 mg/day)	3	28	-16.38	4

performed using data from the exposure (AUC) and PD end point of antimanic activity (YMRS total score) data. Such exposure-response analysis is increasingly recognized as necessary to optimize the benefits of small drug molecules such as endoxifen for patients. As shown in **Figure 4b**, the antimanic effect (response) of endoxifen monotherapy is manifested as the exposure is increased. Regression analysis of YMRS total score and AUC indicates that the relationship was linear, with $R^2 = 0.9559$.

DISCUSSION

This is the first controlled clinical trial that demonstrates that endoxifen, when used alone, significantly ($P < 0.0001$) reduces the manic symptoms associated with BPD I. Endoxifen, at two fixed doses, produced significantly greater improvements on the Young Mania Rating Scale at almost every treatment evaluation. The evidence for efficacy and safety of endoxifen based on the controlled data observed in this trial provide an alternate treatment option to the physician and patients. The efficacy of endoxifen observed in this trial was not significantly different from divalproex, a "the first-line" pharmacological treatment for patients with mania. The duration of this trial (21 days) may be insufficient to adequately make clinical decisions regarding the efficacy and safety of long-term endoxifen treatment in patients with BPD I. Particularly, the effects of endoxifen on weight gain and metabolic parameters should be interpreted with caution.

As shown in **Table 3**, the magnitude of the endoxifen effect at 4 mg/day or 8 mg/day compares favorably with the magnitude of effect shown on the YMRS in recently conducted 3-week monotherapy trials of BPD I with tamoxifen, aripiprazole, and olanzapine.^{6,7,22-25} Similar to other BPD I studies, a 3-week study duration was sufficient to assess endoxifen efficacy in the treatment of BPD I. Due to its PKC inhibitory as well as the antiestrogenic activity of endoxifen, the maximal utilization of this drug may be restricted. However, longer studies are needed to determine the efficacy and tolerability of endoxifen. In conclusion, orally administered endoxifen at 4 mg/day or 8 mg/day in this phase II clinical trial was well

tolerated and showed significant improvement in manic or mixed episodes patients.

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Conflict of Interest/Disclosure. The authors declare no conflicts of interest.

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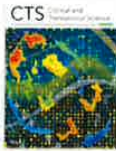
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