Volume 47 • Number 2 • 2017

Psychopharmacology BULLETIN

ORIGINAL RESEARCH

EVIDENCE-BASED MEDICINE

COMPLICATED CASE HISTORIES

MEDWORKS MEDIA®
FOR MORE JOURNALS & BULLETINS VISIT:
www.psychopharmbulletin.com www.medworksmedia.com

Psychopharmacology Bulletin is a trademark of MedWorks Media Inc., Los Angeles, CA. ***Psychopharmacology Bulletin*** is indexed in Index Medicus, EMBASE/Excerpta Medica, Elsevier, Scopus, Psychological Abstracts, Current Contents, Science Citation Index, and Biological Abstracts under *Psychopharmacol Bull*. The journal is also available to medical libraries and repositories through EbscoHost.

***Psychopharmacology Bulletin*: Volume 47 • Number 2 • 2017**

Psychopharmacology Bulletin in Online: ISSN# 2472-2448

Psychopharmacology Bulletin in Print: ISSN# 0048-5764

Psychopharmacology Bulletin is published quarterly by MedWorks Media Inc., 2205 Rockefeller Lane, Bldg. B, Redondo Beach Ca. 90278.
Psychopharmacology Bulletin academic supplements are published on demand.

One-year subscription rates:

In-Training	$250
Individuals	$325
Institutions	$400
Full Access	$500

Secure On-line Subscriptions:
https://medworksmedia.com/product-category/psychopharmacologysub

Portal Addresses:
Home – http://medworksmedia.com
P.B – http://medworksmedia.com/product-category/psychopharmacology-bulletin
T.E.N – http://medworksmedia.com/t-e-n
M.F – http://medworksmedia.com/mental-fitness
P.S.I – http://medworksmedia.com/spanish/psi
Brainscienceblogs – http://medworksmedia.com/brainscienceblogs
Gradworks – http://medworksmedia.com/product-category/pocket reference_guide
Subscriptions – https://medworksmedia.com/product-category/psychopharmacology-sub

MEDWORKS MEDIA
THE VOICE OF SCIENCE

Psychopharmacology Bulletin is a member of the Medscape Publishers' Circle®, an alliance of leading medical publishers whose content is featured on Medscape (http://www.medscape.com). Readers of Psychopharmacology Bulletin can earn AMA P RA Category 1 credits based on selected articles from this journal at Medscape.com. Medscape is part of the WebMD Medscape Health Network for professionals.

Psychopharmacology BULLETIN

Psychopharmacology
BULLETIN

ORIGINAL RESEARCH

EVIDENCE-BASED MEDICINE

COMPLICATED CASE HISTORIES

Aims and Scope

Psychopharmacology Bulletin publishes full-length research articles, review articles, brief reports, clinical case studies, commentary, and letters. Manuscripts submitted to Bulletin's new section, Negative and Failed Clinical Trial Reports will be entitled to fast-track review.

Psychopharmacology Bulletin is committed to the highest ethical standards in medical research. Accordingly, we ask authors to provide specific information regarding ethical treatment of research participants, patient consent, patient privacy, protocols, authorship, and competing interests. We also ask that reports of certain specific types of studies adhere to generally accepted standards. Our requirements are based on the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, issued by the International Committee for Medical Journal Editors. (http://www.icmje.org/)

Manuscript Submission

Manuscript files can be in the following formats: DOC, DOCX, or PDF. Microsoft Word documents should not be locked or protected. An electronic file of manuscripts (including all illustrations and tables) should be submitted to editorial@medworksmedia.com, or sent to MedWorks Media's submission receiving address:

MedWorks Media Inc.
2205 Rockefeller Lane, Bldg. B
Redondo Beach CA. 90278
Tel: 310-374-1300

Manuscripts for consideration by *Psychopharmacology Bulletin* must be submitted solely to *Psychopharmacology Bulletin*, and may not have been published in another publication of any type, professional or lay. Manuscripts will be reviewed by a member of the Editorial Board, depending on the principle topic and focus of the submission. The journal will not be responsible for loss of manuscripts at any time. Upon acceptance of a manuscript for publication, the corresponding author will be required to sign an agreement transferring copyright to the publisher. All such manuscripts become the property of the publisher, and no material published in the journal may be reproduced or published elsewhere without written permission from the publisher, who reserves copyright.

Any possible conflict of interest, financial or otherwise, related to the submitted work must be clearly indicated in the manuscript, or in a cover letter accompanying the submission. All statements in, or omissions from, published manuscripts are the responsibility of the authors, who will be asked to review proofs prior to publication. Reprint order forms will be sent with the page proofs. No page charges will be levied against authors or their institutions for publication in *Psychopharmacology Bulletin*.

Format of Manuscript Elements

Manuscripts must be in English with wide (1 inch) margins, typed and double-spaced throughout. Number pages consecutively. Manuscripts should contain each of the following elements in sequence: 1) title page, 2) abstract, 3) text, 4) acknowledgements, 5) references, 6) tables, and 7) figure legends. Start each subdivision on a new page. Define abbreviations at the first mention in the text. Manuscripts should be prepared using American Medical Association style. Use generic drug names in the text. The text should be written in a uniform style, and its contents as submitted for consideration should be deemed final by the author and suitable for publication as follows:

Title Page

The title page should contain the complete title of the manuscript, author names with degrees, and each author's title(s) and affiliation, institution(s) at which the work was performed, and name, address,

telephone, and tel/fax numbers, and e-mail address of the author responsible for correspondence. Authors should also provide a short title of not more than 45 characters (including spaces), and 5 to 10 key words, not in the title but taken from Index Medicus, that will highlight the subject matter of the article.

Abstract
Abstracts must be 250 words or less, and should be intelligible without reference to the text. Objectives, experimental design, principal observations, and conclusions should be succinctly summarized for research articles, brief reports, and reviews.

Research articles
There are no restrictions on the number of pages or figures. Introduction, Materials and Methods, Results, Discussion, and Conclusion sections conforming to standard scientific reporting style are required (where appropriate, Results and Discussion may be combined). Research articles should include a hypothesis. Detailed information on statistics should be provided such as name of statistical test, whether tests were one- or two-tailed, test used for each set of data, and correction factors, if any, for multiple comparisons. Data and figures should present or reflect standard deviations rather than standard error of means. All significant and relevant nonsignificant results must include test values, degree(s) of freedom, and probability.

Brief reports
Brief reports are intended for presentation of data on research projects which have progressed to a point where preliminary observations should be disseminated (eg, pilot studies, initial drug trials, significant findings in need of replication). Brief reports may not exceed four printed pages (approximately six double-spaced manuscript pages, inclusive of text, references, figures, and legends). Section headings are not necessary. Concise abstracts should be included.

Review articles
Review and theoretical articles are usually invited, but submitted reviews or theory-oriented articles will be considered. Such articles should provide a critical review and interpretation of the literature and current research directions in a given area. An abstract is required. The text should flow smoothly, and subdivisions (eg, Introduction, Methods, Results) within the manuscript are not necessary. There are no a priori page limitations for reviews or theoretical papers; however, proposals for papers of this nature should be directed to the *Psychopharmacology Bulletin* editor, who will consult with the author before manuscript submission.

Clinical case studies
Clinical case reports should comprise two to four printed pages (approximately 4–6 manuscript pages including illustrations and tabular material). Studies should be divided into the following sections: Case History, Symptomatology, Diagnosis, Treatment, and Discussion. Presentation of clinical data should be accompanied by appropriate patient releases/permissions.

Peer-reviewed letters
Letters are encouraged as a mechanism for rapid communication of novel observations or important research findings; however, space limitations do not enable the journal to publish all letters received. Letters are also welcomed from readers who wish to comment on investigations within the editorial scope and content of *Psychopharmacology Bulletin*. Opinions and views expressed by authors in letters to the editor are their own and do not necessarily reflect the views of the MedWorks Media publisher James M. La Rossa Jr., the editor Dr. Michael E. Thase, or the editorial advisory board. All submissions will be peer-reviewed, and may be altered for space or clarity. Letters should be

typewritten double-spaced, and should not exceed 1,000 words of text, although exceptions may be made at the discretion of the editor. References should be held to a minimum. Letters referring to a recent *Psychopharmacology Bulletin* article shall not exceed 500 words and must be received within 6 weeks of the article's publication. Letters must not duplicate other material published or submitted for publication. A signed statement for transfer of copyright, authorship responsibility, and financial disclosure is essential for publication.

References
References should be submitted in American Medical Association style. Please see the following examples:

Journal:
Londos E, Passant U, Brun A, Gustafson L. Clinical Lewy body dementia and the impact of vascular components. Int J Geriatr Psychiatry. 2000;15(1):40-49.

Book:
Schatzberg AF, Nemeroff CB, eds. Textbook of Psychopharmacology. 2nd ed. New York, NY: APA Press; 1998:155-169.

Chapter in book:
Weissman M, Klerman G. Interpersonal psychotherapy for depression. In: Wolman B, Stricker G, eds. Depressive Disorders: Facts, Theories, and Treatment Methods. New York, NY: John Wiley & Sons Inc.; 1990:379-395.

References should be listed in order of appearance at the end of the text and represented in the text using the corresponding reference numbers.

Tables
Each table must have a title and should be self-explanatory. Avoid duplicating information in the text. Number tables with Arabic numerals in order of appearance in the text.

Illustrations
Illustrations should be numbered consecutively using Arabic numerals and should include the name of the author(s), manuscript title, and illustration number.

Each figure requires a corresponding legend; legends should be double-spaced. Each legend should describe briefly the information presented; detailed descriptions of results or procedures should appear in the Results or Materials and Methods sections. Abbreviations used in figures and photographs must match exactly those used in the text. Do not write directly on glossy prints, front or back, and do not use devices such as paper clips, which might scratch or dent photographic prints. Authors are encouraged to submit color illustrations that highlight the text and convey essential scientific information. For best reproduction, bright, clear colors should be used. Dark colors against a dark background do not reproduce well; please place your color images against a white background wherever possible.

ORIGINAL RESEARCH

Key Words: atypical antipsychotics, antipsychotics, cardiovascular disease, metabolic syndrome, schizophrenia, sex differences

Sex Differences in Antipsychotic Related Metabolic Functioning in Schizophrenia Spectrum Disorders

By A. Zarina Kraal, Kristen M. Ward, Vicki L. Ellingrod

ABSTRACT *~ The adverse metabolic risks associated with second generation antipsychotics (SGAs) are well known, and likely contribute to the high rate of premature mortality due to cardiovascular disease in schizophrenia. Female schizophrenia patients appear to be diagnosed with metabolic diseases at higher rates than males, which may reflect disparate adverse responses to SGAs. However, the relationship between sex, metabolic risk, and drug use is less developed. We aimed to explore this relationship further by identifying rates of metabolic disease in community dwelling schizophrenia patients by sex and SGA risk. Schizophrenia participants (N = 287, 40.4% female) were included in this analysis. Oneway-ANOVA and Fisher's Exact Test were used to compare groups, as appropriate, and Cohen's d was employed to estimate the effect size of sex. In the group as a whole, the rate of metabolic syndrome was higher than previously reported, but did not differ by sex. For females, greater metabolic disturbances across all medication risk groups were seen in BMI and waist circumference ($p < 0.005$) but most commonly in those receiving high risk medication (clozapine or olanzapine). Additionally, the number of participants receiving medications for these metabolic disturbances was extremely low (<30%). These results suggest that female schizophrenia patients taking clozapine or olanzapine represent a group at uniquely high risk for metabolic dysfunction and future adverse cardiovascular outcomes, and warrant close monitoring by clinicians to prevent worsening of metabolic risk through proper monitoring and interventions.* Psychopharmacology Bulletin. *2017;47(2):8–21.*

Introduction

Cardiovascular disease (CVD) is a primary cause of mortality among individuals with schizophrenia spectrum disorders, with up to 30 years of life lost compared to the general population.[1,2] Although CVD occurrence is undeniably multifactorial, antipsychotic use may increase CVD risk due to greater risk of specific metabolic abnormalities.[3–5] In particular, the second generation antipsychotics

Ms. Kraal, University of Michigan, Department of Psychology, Ann Arbor, MI, USA. Dr. Ward, University of Michigan, College of Pharmacy, Ann Arbor, MI, USA. Dr. Ellingrod, University of Michigan, College of Pharmacy, Ann Arbor, MI, USA.

To whom correspondence should be addressed: Dr. Vicki L. Ellingrod, University of Michigan, College of Pharmacy, 428 Church St., Ann Arbor, MI 48109 USA. E-mail: vellingr@med.umich.edu

(SGAs) are associated with weight gain leading to obesity, especially abdominal obesity; dyslipidemias such as hypercholesterolemia, hypertriglyceridemia, low high density lipoprotein (HDL), and elevated low density lipoprotein (LDL); and, impaired glucose homeostasis such as hyperglycemia, insulin resistance, and type 2 diabetes mellitus.

Overall, up to 50% of patients receiving SGAs have been reported to meet metabolic syndrome criteria, which substantially increases the risk of CVD morbidity and mortality.[6] In general, metabolic syndrome can be diagnosed when three of five criteria are met that focus on specific cardiovascular risk factors such as abdominal obesity, low high-density lipoprotein (HDL), elevated triglycerides (TG), hypertension, and impaired fasting plasma glucose.[7] In looking at the findings from the Clinical Antipsychotics Trials of Intervention Effectiveness (CATIE), the largest clinical trial of antipsychotics to date, specific sex differences were noted in metabolic risk as females had a higher prevalence and risk for metabolic syndrome compared with males (36.6% and 54.2%, respectively).[8] Although research fousing on sex related differences for metabolic syndrome in the population have been ongoing, results are mixed.[9–11]

Most work focusing on sex related differences in metabolic syndrome risk are typically limited to participants within inpatient settings, limiting 'real world' generalizability. Therefore, the primary aim of this study was to examine differences in metabolic functioning between community dwelling females and males, investigating specific antipsychotic (AP) medication related risks. We hypothesized that females would have worse metabolic functioning and a greater prevalence of metabolic syndrome compared to males, and that this risk would be commensurate with overall AP metabolic risk profiles.

Materials and Method

Participants

Participants were part of a larger study investigating pharmacogenetics predictors of CVD risk related to antipsychotic use and were recruited from the community and outpatient clinics primarily via advertisements. They were included if they: 1) had a DSM-IV diagnosis of schizophrenia, schizoaffective, or psychotic disorder not otherwise specified (American Psychiatric Association, 2000), 2) aged 18 to 90, and 3) receving antipsychotic treatment for at least six months with no significant recent medication changes. Participants were excluded if they were: 1) unable or unwilling to provide informed consent, 2) diagnosed with Type 2 diabetes mellitus prior to antipsychotic treatment, 3) had

a substance dependence disorder, or 4) currently pregnant or nursing. The inclusion criteria were broad to represent 'real world' ambulatory practice. The study was approved by the: University of Michigan Medical School Institutional Review Board, Washtenaw County Health Organization, Ann Arbor Veterans Affairs Medical Center, and Detroit-Wayne County Community Mental Health Agency, and is registered at clinicaltrials.gov (NCT00815854). This study was conducted in accordance with the latest version of the Declaration of Helsinki. Participants were assessed at the Michigan Clinical Research Unit at the University of Michigan.

Procedure

Participants provided written informed consent after the study procedures had been explained. Participants fasted for 8 hours prior to enrolling in the study and all assessments were completed in one visit. The blood draw assessed glucose and lipids. The physical examination assessed vital signs, height, weight, and hip and waist circumferences. Body mass index (BMI) and waist-to-hip ratio (WHR) were calculated from these measurements. The National Cholesterol Education Program's Adult Treatment Panel III[7] criteria were used to diagnose metabolic syndrome.

The clinical interview included a psychiatric diagnostic assessment using the Structured Clinical Interview for DSM IV Axis I Disorders,[12] current and past medication history, and demographics.

Data Analysis

Participants were divided into three AP metabolic risk groups: 1) high – clozapine and olanzapine; 2) moderate – quetiapine, risperidone, paliperidone, and iloperidone; 3) low – all other antipsychotics. This grouping is based on reports in the literature regarding the specific medications' propensities for metabolic disturbances.[13–15]

Analyses on categorical variables were conducted using Fisher's Exact Test and a oneway-ANOVA for continuous variables. Cohen's *d* was used to calculate the effect size of sex. Analyses on the prevalence of metabolic syndrome included the entire sample. Participants prescribed a lipid medication were excluded from analyses on lipid variables. Participants receiving treatment for diabetes were excluded from analyses on plasma glucose. Given its weight controlling properties, analyses on BMI, waist circumference, and WHR excluded participants on an oral hypoglycemic (e.g., metformin). Participants receiving treatment for hypertension were excluded from analyses on blood pressure.

The exclusions are important methodologically, as these medications may attenuate the metabolically negative impact of the APs and therefore limit efforts to determine medication specific sex based differences. A p-value of <0.05 was considered significant.

Results

Overall, 287 participants were included, comprising 116 (40.4%) females with a mean age of 46.90 ± 11.34 (males: 44.16 ± 11.34 years, $p > 0.05$). Table 1 lists participant characteristics and rates of medication use. There were no differences in psychotropic exposure between males and females except in the high risk group in which females were on marginally more medications than their male counterparts. Overall antipsychotic exposure was calculated using chlorpromazine equivalents,[16] which was not different between sexes.

Prevalence and Sex Differences of Metabolic Syndrome

The prevalence of metabolic syndrome in the overall sample was 49.1% with a higher prevalence in females compared to males (52.6% and 46.8%, respectively, $p = 0.12$). This prevalence was highest among participants in the high risk group (64.6%) although there was no sex difference (64.3% females and 64.7% males; $p = 0.58$). In the moderate risk group, metabolic syndrome prevalence was 41.1%, with a higher rate trend in females (52.5%) than males (34.7%), ($p = 0.05$). In the low risk group, metabolic syndrome prevalence was 45.8%, with no sex differences, $p = 0.58$. Table 2 contains values for the overall sample ($N = 287$) stratified by metabolic risk group.

Sex Differences in Metabolic Syndrome Components

Body Composition, Visceral Adiposity, and Fasting Plasma Glucose

In the overall sample of participants not on an oral hypoglycemic ($n = 227$), both females and males were obese on average (BMI $\geq$ 30 kg/m^2 (Table 3)). In particular, females had greater BMIs and higher abnormal waist circumference (WC) and waist-to-hip ratio (WHR) compared to males. These BMI sex differences were greatest in the high risk group ($F(1, 59) = 8.59, p = 0.005$,) and resulted in a fairly robust effect size ($d = 0.7$). A similar pattern though in smaller magnitude was seen in the low risk group ($F(1, 68) = 5.39, p = 0.023, d = 0.5$).

Abdominal obesity (WC $\geq$ 102 cm for males and $\geq$ 90 cm in females and WHR $\geq$ 0.90 in males and $\geq$ 0.80 in females)(NHLBI, 1998), was seen in 69.4% of participants without oral hypoglycemic treatment,

TABLE 1

Participant Characteristics

	WHOLE SAMPLE		HIGH RISK GROUP[a]		MODERATE RISK GROUP[b]		LOW RISK GROUP[c]	
	MALE (n = 171)	FEMALE (n = 116)	MALE (n = 51)	FEMALE (n = 28)	MALE (n = 72)	FEMALE (n = 40)	MALE (n = 48)	FEMALE (n = 48)
Age (M ± SD)	44.16 ± 11.34	46.89 ± 11.34	45.90 ± 11.16	47.18 ± 12.60	41.26 ± 11.41	47.30 ± 9.45**	46.65 ± 10.67	46.40 ± 12.22
Racial Distribution								
%White	50.9	56	60.8	67.9	41.7	45	54.2	58.3
%Black	40.9	27.6	31.4	14.3	50	37.5	37.5	27.1
%Other	8.2	6.4	7.8	17.3	8.3	17.5	8.6	14.6
Diagnosis								
%SCZP/SCZA/NOS			68.6/27.5/3.9	39.3/57.1/3.6	45.8/41.7/12.5	30.0/57.5/12.5	39.6/43.8/16.7	27.1/64.6/8.3
% Lipid Medication	28.7	28.4	49	32.1	19.4	25	20.8	29.2
% BP Medication	33.3	33.6	41.2	25	26.4	35	35.4	37.5
% DM Medication	19.3	22.4	19.6	21.4	15.3	17.5	25	27.1
CPZE	727.5 ± 765.2	644.0 ± 746.3	791.4 ± 770.7	833.0 ± 829.8	736.7 ± 711.0	656.8 ± 582.7	648.2 ± 837.8	518.2 ± 805.0
Psychotropic Medications (M ± SD)	2.44 ± 1.13	2.85 ± 1.30	2.31 ± 1.10	2.89 ± 1.29*	2.53 ± 0.93	2.80 ± 1.38	2.46 ± 1.41	2.85 ± 1.25

Notes: **$p < 0.01$. *$p < 0.05$. [a]High Risk Group = clozapine or olanzapine. [b]Moderate Risk Group = quetiapine, risperidone, iloperidone, or paliperidone. [c]Low Risk Group = all other antipsychotics.

Abbreviations: BP, blood pressure; CPZE, chlorpromazine equivalence; DM, Type 2 diabetes mellitus; M, Mean; NOS, psychosis not otherwise specified; SCZP, schizophrenia; SCZA, sczhioaffective disorder; SD, standard deviation.

TABLE 2

Prevalence of Metabolic Syndrome and its Components

	WHOLE SAMPLE		HIGH RISK GROUP[a]		MODERATE RISK GROUP[b]		LOW RISK GROUP[c]	
MetS VARIABLES	MALE (n = 171)	FEMALE (n = 116)	MALE (n = 51)	FEMALE (n = 28)	MALE (n = 72)	FEMALE (n = 40)	MALE (n = 48)	FEMALE (n = 48)
% MetS	46.8	52.6	64.7	64.3	34.7	52.5*	45.8	45.8
% Abdominal Obesity	60.4	91.4***	69.4	96.4***	58.3	92.5***	54.2	87.5***
% Hypertension	43.3	37.9	54.9**	32.1	31.9	42.5	47.9	37.5
% Elevated Triglycerides	48.2	45.7	66.7	57.1	37.7	45	43.8	39.6
% Low HDL	47.3	51.7	68.6	53.6	35.7	45	41.7	56.3
% Elevated FPG	45.6	45.7	52.9	53.6	36.1	45	52.1	41.7

Notes: *$p < 0.1$. **$p < 0.05$. ***$p < 0.01$. [a]High Risk Group = clozapine or olanzapine. [b]Moderate Risk Group = quetiapine, risperidone, iloperidone, or paliperidone. [c]Low Risk Group = all other antipsychotics.
Abbreviations: FPG, fasting plasma glucose; HDL, high density lipoprotein; MetS, metabolic syndrome.

comprising 87.4% of females and 57.8% of males, $p < 0.001$. Higher rates of abdominal obesity in females compared to males were seen across the three metabolic risk groups (Table 3; Figure 1).

For WHR, 97.7% of females and 77.8% of males ($n = 227$; $p < 0.001$) met or exceeded this criterion. Notably, 100% of females in the high and moderate metabolic risk groups and 93.9% of females in the low risk group had abnormal WHR compared to 74.2%–83.8% of males across the metabolic risk groups. These striking results trended towards significance ($p \leqslant 0.06$ for all), and are highlighted for their clinical relevance. Although few sex differences in fasting plasma glucose were seen overall, males in the low risk group alone had higher fasting plasma glucose compared to females ($F(1, 67) = 4.92$, $p = 0.03$), resulting in a moderate effect size ($d = 0.5$). The average fasting plasma glucose for all groups was <100 mg/dL, suggesting that these differences may not be clinically significant. In terms of clinical significance, however, more than twice as many males (36.1%) than females (17.6%), $p = 0.04$, had fasting plasma glucose levels at or above the risk level.

Hypertension

For hypertension, in the overall sample of participants not on an antihypertensive ($n = 190$), males had higher diastolic BP (dBP) compared to females ($F(1, 188) = 9.76$, $p = 0.02$), with a moderately sized sex effect, $d = 0.46$ (Table 3). Stratified by metabolic risk group, a larger effect of sex was found, showing higher dBP in males than females in the high ($F(1, 48) = 4.03$, $p = 0.05$), $d = 0.57$ and low ($F(1, 59) = 12.93$, $p = 0.001$), $d = 0.92$ risk groups (Table 3). Males in the low risk group alone also had higher systolic BP (sBP) compared to

TABLE 3

Results from Analyses on Lipid, Anthropometric, Glucose Dysregulation, and Blood Pressure Variables

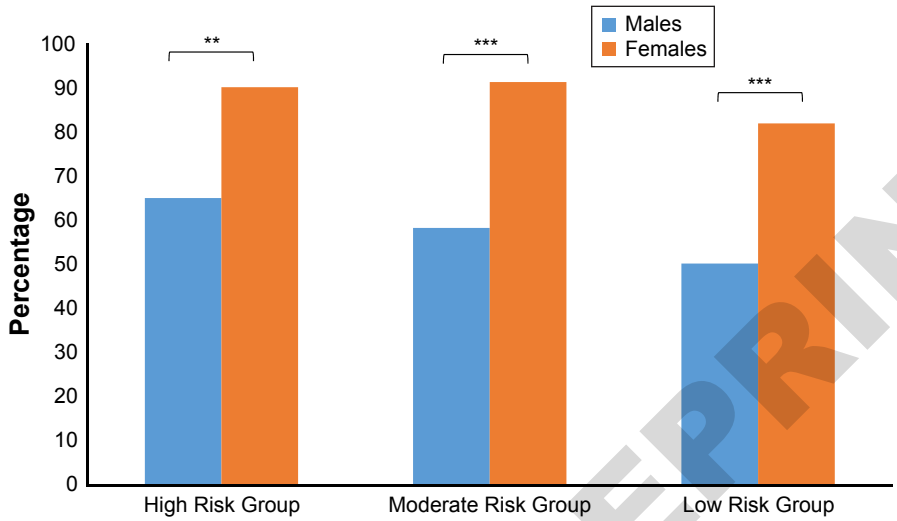
	WHOLE SAMPLE		HIGH RISK GROUP[a]		MODERATE RISK GROUP[b]		LOW RISK GROUP[c]	
	MALE (n = 118)	FEMALE (n = 80)	MALE (n = 26)	FEMALE (n = 18)	MALE (n = 54)	FEMALE (n = 29)	MALE (n = 38)	FEMALE (n = 33)
Total Cholesterol (mg/dL)	172.46 ± 39.46	190.74 ± 38.41**	173.12 ± 37.54	196.39 ± 37.22**	170.13 ± 36.5	195.59 ± 43.46***	175.32 ± 45.23	183.39 ± 34.04
HDL (mg/dL)	50.14 ± 15.88	61.31 ± 18.78***	45.96 ± 15.4	61.06 ± 17.89***	50.91 ± 14.68	63.14 ± 19.83***	51.92 ± 17.68	59.85 ± 18.75*
LDL (mg/dL)	109.67 ± 34.78	122.19 ± 35.03*	109.85 ± 31.41	127.83 ± 38.56*	108.85 ± 28.09	121.35 ± 35.32*	110.71 ± 45.01	119.85 ± 33.52
Triglycerides (mg/dL)	125.70 ± 91.13	118.24 ± 94.29	147.77 ± 120.42	113.33 ± 40.20	110.69 ± 73.36	134.59 ± 117.91	131.92 ± 89.67	106.55 ± 92.36
	MALE (n = 138)	FEMALE (n = 89)	MALE (n = 40)	FEMALE (n = 21)	MALE (n = 54)	FEMALE (n = 29)	MALE (n = 38)	FEMALE (n = 33)
BMI (kg/m^2)	30.40 ± 6.50	34.03 ± 8.79***	30.17 ± 4.83	35.44 ± 9.28***	31.09 ± 7.27	32.88 ± 6.64	29.48 ± 6.75	34.33 ± 10.35**
% WC	58.1	88.8***	64.9	90**	58.1	91.2***	50	81.8***
% WHR	77.8	97.7***	83.8	100*	74.2	100***	77.8	93.9*
FPG (mg/dL)	98.07 ± 31.20	93.80 ± 13.62	94.65 ± 10.61	97.48 ± 15.89	100.34 ± 44.83	94.41 ± 14.39	98.17 ± 15.80**	90.88 ± 10.79
			MALE (n = 29)	FEMALE (n = 21)	MALE (n = 54)	FEMALE (n = 29)	MALE (n = 38)	FEMALE (n = 33)
Diastolic BP (mm/Hg)	75 ± 11.13	69.88 ± 11.01**	76.28 ± 11.21*	69.33 ± 13.2	72.81 ± 10.2	72.65 ± 11.52	77.5 ± 12.16***	67.87 ± 8.48
Systolic BP (mm/Hg)	122.10 ± 14.84	118.50 ± 17.70	121.93 ± 16.54	119.38 ± 22.31	120.91 ± 17.62	122.12 ± 17.62	124.29 ± 13.42***	114.73 ± 13.54

Notes: ***$p < 0.001$. **$p < 0.01$. *$p < 0.05$. [a]High Risk Group = clozapine or olanzapine. [b]Moderate Risk Group = quetiapine, risperidone, iloperidone, or paliperidone. [c]Low Risk Group = all other antipsychotics. %WC, percent of participants with waist circumference ⩾ 102cm for males and ⩾ 90 cm in females; %WHR, percent of participants with waist-to-hip ratio ⩾ 0.90 in males and ⩾ 0.80 in females.

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index; FPG, fasting plasma glucose; BP, blood pressure.

FIGURE 1

Percentage of Participants Meeting Criteria for Abdominal Obesity by Sex



Notes: $^{***}p < 0.001$. $^{**}p < 0.01$. $^{*}p < 0.05$. High Risk Group = clozapine or olanzapine. Moderate Risk Group = quetiapine, risperidone, iloperidone, or paliperidone. Low Risk Group = all other antipsychotics. Abdominal obesity was defined by waist circumference and percentages represent those with waist circumference ⩾102 cm for males and ⩾90 cm in females.

females, ($F(1, 59) = 7.67$, $p = 0.008$), $d = 0.71$. However, these differences were considered clinically non-significant as dBP and sBP values were below the threshold for hypertension diagnosis.

Lipids

The lipids analyses stratified by metabolic risk group examined total cholesterol (TC), triglycerides, LDL, and HDL. As lipid levels may be impacted by age,[18] and slight sex differences in age were identified in the moderate risk group, a series of regressions were conducted to determine the impact of age and sex on predicting lipid laboratory values. No significant differences were noted and analyses were carried out as planned.

In the overall sample of participants not on dyslipidemia medication ($n = 198$), females had higher TC than males, ($F(1, 196) = 10.45$, $p = 0.001$), with a medium sized effect, $d = 0.50$. Stratified by metabolic risk group, higher TC in females than males carried across the high ($F(1, 42) = 4.12$, $p = 0.049$, $d = 0.6$) and moderate ($F(1, 81) = 8.02$, $p = 0.006$, $d = 0.94$) risk groups, with a larger sex effect. Although average TC values fell below the risk threshold (<200 mg/dL), and males' average TC across the three risk groups were normal and relatively

similar (170.13–175.32 mg/dl), females in the high and moderate risk groups (195.59–196.39 mg/dl), were much closer to the risk threshold. Additionally, the prevalence of high TC (⩾200 mg/dL) was more than twice as high among females (41.4%–50.0%) compared to males (18.5%–19.2%) in the high and moderate risk groups ($p < 0.03$ for all).

In addition to TC, higher LDL levels in females compared to males were found in the overall sample, ($F(1, 196) = 6.14$, $p = 0.01$), with a small sex effect, $d = 0.36$. Average LDL levels were within normal range across groups but females' levels approached the risk threshold (⩾130 mg/dL) whereas males' did not, specifically in the high, and to a lesser extent, moderate risk groups (Table 3).

Although sex differences in HDL levels were found in the overall sample as well as the metabolic risk groups (Table 3), these were expected due to known sex differences (Grundy et al., 2004). No sex differences were found in the prevalence of low HDL but notably, 28.6% of the sample (47% female and 53.0% males) met the criterion.

Discussion

This study investigated medication related sex differences in metabolic measures in individuals with schizophrenia spectrum disorders on long term AP treatment within the community. Within the whole sample (i.e., no treatment exclusions) almost 50% of participants met criteria for metabolic syndrome, with higher rates seen in the high risk medication group regardless of sex (Table 2). These findings contrast CATIE which showed a lower prevalence of metabolic syndrome overall (42.7%; McEvoy et al., 2005), and a higher prevalence in females compared to males. However approximately 14% of our participants were receiving clozapine relative to none of the participants in the CATIE trial. The higher incidence of metabolic syndrome within the high risk groups is also higher than that found in other studies of individuals on clozapine or olanzapine[10,19] and suggest that long term use of such drugs may pose a higher metabolic risk than previously reported.

Results excluding those diagnosed and receiving treatment for glucose, blood pressure, or lipid dysregulation revealed more nuanced sex differences. To our knowledge this investigation is the first to conduct analyses specifically excluding those receiving current treatment for these conditions, which is important, as these medications may attenuate the metabolically negative impact of the APs and therefore limit efforts to determine medication specific sex based differences. Overall, 70% of our participants were not receiving an oral hypoglycemic (n = 227) and compared to males, females had greater BMI, higher rates of abnormal WC and WHR, and greater dysregulation of TC and LDL. Importantly,

high risk group females had the greatest risk across all metabolic factors considered, whereas there was more variability in the type and severity of risk factors among females in the moderate and low risk groups. Thus, females in the high risk group appear to be at greatest risk for metabolic syndrome and overall CVD. In general, these findings were in line with expectations. Males, however, had higher fasting plasma glucose levels as well as higher diastolic and systolic blood pressure, with the greatest sex effect seen in the low risk group, contrary to expectations. Our findings regarding the females were somewhat expected given the widely known weight gain propensity of clozapine and olanzapine (Klemettilä et al., 2014; Taylor and McAskill, 2000). However, higher BMI in females than males in the low risk group has not been previously reported.

Results in WC and WHR also aligned with predictions, lending further credence to reports showing that visceral adiposity markers are predictive of AP associated CVD risk, especially compared to BMI.[22] More females had elevated WC and WHR compared to males across the three risk groups which parallels results from other groups[10,23] and provides further evidence that females are at greater risk for AP associated visceral adiposity,[7] insulin resistance, diabetes, and coronary artery disease risk[17,24–26] and is a predictor of CVD mortality.[27,28] The striking finding from this analysis is that 100% of females in the high and moderate risk groups met central adiposity criterion (WHR $>$ 0.8) which is clinically significant, suggesting an important sex-specific risk to consider in long term AP therapy. Overall, our findings confirm that an overwhelmingly large proportion of individuals with schizophrenia spectrum disorders prescribed antipsychotic medication are at risk for obesity and visceral adiposity, which may be worsening despite available monitoring guidelines that recommend routine BMI measurements.[29] Though not specifically outlined in the monitoring guidelines, obtaining routine waist and hip circumferences may be useful for medication management in the context of cardiovascular health and should be considered, especially for females.

Sex differences were also seen in fasting plasma glucose, where low risk group males had higher values compared to female counterparts. Although the average was below the current diabetes risk threshold ($<$100 mg/dL), it is important to note that twice as many males (36.1%) than females (17.6%) met the criterion. This finding may also point to a nontrivial lack of preventive screening and treatment for elevated glucose within the low risk group. As 40.5% of those in the high risk group and 31.1% in the moderate risk group had an elevated glucose, adhering to metabolic monitoring guidelines, which recommends annual checks is critical. Since only 21% of participants were

receiving an oral hypoglycemic agent at study assessment, our findings of widespread non-specific glucose dysregulation are clinically significant and also highlight the need for continued metabolic monitoring.

For our hypertension analysis, 66% (n = 190) of study participants were included, as 34% were currently receiving hypertension treatment. Given the APs' intrinsic antagonistic action on adrenergic receptors, we expected higher values in all medication groups for males than females due to known sex differences in regulation (for a review, see Reckelhoff, 2001).[30] However, although males had higher dBP in the high risk group and higher dBP and sBP in the low risk group the average dBP and sBP values seen in both males and females fell within normal range, suggesting that blood pressure dysregulation may not be a sex-specific concern associated with AP maintenance therapy. Regardless, blood pressure should be routinely assessed, especially for those on SGAs in the high and moderate risk groups given their weight gain propensity.

Sex differences were also found in regards to lipids, with females having higher TC and LDL and males having lower HDL. This analysis included 70% (n = 189) of our total study participants, as the others were currently receiving a lipid lowering agent. Nervertheless, these findings are similar to our group's previous work,[31] except this current study further explores sex differences stratified by AP risk for metabolic disturbances. Specifically, within the high and moderate risk groups, females had higher TC than males. Most notably, the prevalence of abnormal TC ($\geqslant$ 200 mg/dL) was much more common in females (41.4–50%) compared to males (18.5–19.2%) in the high and moderate risk groups.

Similarly, higher LDL in females was found in the high and moderate risk groups with females approaching the threshold of borderline high whereas values in males were closer to the "normal" range. This clinically significant finding parallels other research showing increased LDL associated with AP use especially in clozapine and olanzapine therapy.

Overall males had lower HDL levels than females in the three groups which has been previously reported,[20] although conflicting literature does exist.[8,10,23] Therefore, comparisons between findings here and those in other studies must be done cautiously.

Altogether, our results suggest that both females and males are at risk for medication specific lipid dysregulation and that these findings may be especially beneficial for clinicians to consider when initiating and maintaining antipsychotic therapy.

Limitations

Although this study revealed important findings, there are some limitations to be acknowledged. Firstly, the cross-sectional design of the

study limits a definitive causal relationship on sex, AP use, and metabolic parameters. Secondly, APs were analyzed in groups rather than in isolation due to sample size constraints. However, APs in each group have very similar metabolic risk propensity and participants had been using these medications chronically and were stable on them. Future research with large sample sizes should examine these APs individually. Lastly, p-value corrections for multiple comparisons were not used given a priori hypotheses and in order to decrease the likelihood of committing Type II error.

Conclusion

Based on our data we present three primary conclusions. Firstly, the prevalence of metabolic syndrome among those on maintenance AP therapy is notably high, especially among those in the high risk medication group, and this estimate may be higher than previously reported. Secondly, with respect to sex, females on APs considered to confer high or moderate metabolic risk appear to have the highest levels of metabolic dysfunction, specifically dyslipidemia and central adiposity, both of which increase risk for metabolic syndrome and overall CVD. Importantly, females on clozapine or olanzapine appear to represent a very high risk group for metabolic dysfunction and CVD, which has been previously reported. Conversely, males on these medications appear to be at highest risk for low HDL only. Clinicians should take note of these findings and consider the benefit-risk tradeoff when prescribing APs. In addition, preventative screening and adjunctive interventions aimed at decreasing risk for metabolic dysfunction should be utilized to help attenuate risks. As approximately 35% of participants were prescribed medications for the treatment of hypertension, dyslipidemia, or glucose dysregulation, this study suggests a striking lack of metabolic monitoring, which unfortunately parallels other research which concludes that adherence to the monitoring guidelines is poor.[32,33] ✤

Acknowledgements

The authors thank the staff and consumers at the Washtenaw County Health Organization, Ann Arbor Veterans Affairs Medical Center, and the Detroit-Wayne County Community Mental Health Agency for their assistance and participation, respectively, in the current study. In addition, this study was supported by grants from The National Institute of Mental Health (R01MH082784), the National Center for Advancing Translational Sciences of the National Institutes of Health

(2UL1TR000433-06), and the Chemistry Core of the Michigan Diabetes Research and Training Center (DK020572) from the National Institute of Diabetes and Digestive and Kidney Diseases.

Conflict of Interest

All authors declare that they have no conflicts of interest.

Role of Funding Source

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev Chronic Dis*. 2006;3(2):A42. doi:A42 [pii].
2. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch Gen Psychiatry*. 2007;64(10):1123–1131. doi:10.1001/archpsyc.64.10.1123.
3. Asmal L, Flegar SJ, Wang J, Rummel-Kluge C, Komossa K, Leucht S. Quetiapine versus other atypical antipsychotics for schizophrenia. In: Asmal L, ed. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2013:CD006625. doi:10.1002/14651858.CD006625.pub3.
4. Meyer JM, Davis VG, Goff DC, et al. Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE Schizophrenia Trial: Prospective data from phase 1. *Schizophr Res*. 2008;101(1–3):273–286. doi:10.1016/j.schres.2007.12.487.
5. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs*. 2005;19 Suppl 1:1–93.
6. Meyer JM, Koro CE. The effects of antipsychotic therapy on serum lipids: a comprehensive review. *Schizophr Res*. 2004;70(1):1–17. doi:10.1016/j.schres.2004.01.014.
7. Grundy SM, Brewer HB, Cleeman JI, Smith SC, Lenfant C. Definition of metabolic syndrome: report of the national heart, lung, and blood institute/american heart association conference on scientific issues related to definition. *Circulation*. 2004;109(3):433–438. doi:10.1161/01.CIR.0000111245.75752.C6.
8. McEvoy JP, Meyer JM, Goff DC, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: Baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. *Schizophr Res*. 2005;80(1):19–32. doi:10.1016/j.schres.2005.07.014.
9. Fan X, Liu EY, Freudenreich O, et al. Higher white blood cell counts are associated with an increased risk for metabolic syndrome and more severe psychopathology in non-diabetic patients with schizophrenia. *Schizophr Res*. 2010;118(1–3):211–217. doi:10.1016/j.schres.2010.02.1028.
10. Hägg S, Lindblom Y, Mjörndal T, Adolfsson R. High prevalence of the metabolic syndrome among a Swedish cohort of patients with schizophrenia. *Int Clin Psychopharmacol*. 2006;21(2):93–98.
11. Lamberti JS, Olson D, Crilly JF, et al. Prevalence of the metabolic syndrome among patients receiving clozapine. *Am J Psychiatry*. 2006;163(7):1273–1276. doi:10.1176/appi.ajp.163.7.1273.
12. First MB, Spitzer R, Gibbon M, Williams J. *Structured Clinical Interview for DSM-IV Axis I Disorders SCID-I: Clinician Version, Administration Booklet*. American Psyciatric Press; 1997.
13. Correll CU, Lencz T, Malhotra AK. Antipsychotic drugs and obesity. *Trends Mol Med*. 2011;17(2):97–107. doi:10.1016/j.molmed.2010.10.010.
14. De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol*. 2012;8(2):114–126. doi:10.1038/nrendo.2011.156.

15. Ventriglio A, Gentile A, Stella E, Bellomo A. Metabolic issues in patients affected by schizophrenia: Clinical characteristics and medical management. *Front Neurosci*. 2015;9(SEP). doi:10.3389/fnins.2015.00297.
16. Andreasen NC, Pressler M, Nopoulos P, Miller D, Ho B-C. Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. *Biol Psychiatry*. 2010;67(3):255–262. doi:10.1016/j.biopsych.2009.08.040.
17. NHLBI Obesity Education Initiative Expert Panel on the Identification E and T of O in A (US). Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. 1998.
18. Upmeier E, Lavonius S, Heinonen P, et al. Longitudinal changes in serum lipids in older people the Turku Elderly Study 1991–2006. *Age Ageing*. 2011;40(2):280–283. doi:10.1093/ageing/afq180.
19. Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W, De Hert M. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders–a systematic review and meta-analysis. *Schizophr Bull*. 2013;39(2):306–318. doi:10.1093/schbul/sbr148.
20. Klemettilä JP, Kampman O, Seppälä N, et al. Cytokine and adipokine alterations in patients with schizophrenia treated with clozapine. *Psychiatry Res*. 2014;218(3):277–283. doi:10.1016/j.psychres.2014.04.049.
21. Taylor DM, McAskill R. Atypical antipsychotics and weight gain–a systematic review. *Acta Psychiatr Scand*. 2000;101(6):416–432.
22. de Vegt F, Dekker JM, Jager A, et al. Relation of Impaired Fasting and Postload Glucose With Incident Type 2 Diabetes in a Dutch Population. *Jama*. 2001;285(16):2109. doi:10.1001/jama.285.16.2109.
23. Bobes J, Arango C, Aranda P, Carmena R, Garcia-Garcia M, Rejas J. Cardiovascular and metabolic risk in outpatients with schizophrenia treated with antipsychotics: Results of the CLAMORS Study. *Schizophr Res*. 2007;90(1–3):162–173. doi:10.1016/j.schres.2006.09.025.
24. Albu JB, Murphy L, Frager DH, Johnson JA, Pi-Sunyer FX. Visceral fat and race-dependent health risks in obese nondiabetic premenopausal women. *Diabetes*. 1997;46(3):456–462. doi:10.2337/diabetes.46.3.456.
25. Burghardt K, Goodrich J, Dolinoy D, Ellingrod V. DNA methylation, insulin resistance and second-generation antipsychotics in bipolar disorder. *Epigenomics*. 2015;7(3):343–352. doi:10.2217/epi.15.5.
26. Ellingrod VL, Taylor SF, Brook RD, et al. Dietary, lifestyle and pharmacogenetic factors associated with arteriole endothelial-dependent vasodilatation in schizophrenia patients treated with atypical antipsychotics (AAPs). *Schizophr Res*. 2011;130(1–3):20–26. doi:10.1016/j.schres.2011.03.031.
27. Folsom AR, Stevens J, Schreiner PJ, McGovern PG. Body mass index, waist/hip ratio, and coronary heart disease incidence in African Americans and whites. Atherosclerosis Risk in Communities Study Investigators. *Am J Epidemiol*. 1998;148(12):1187–1194.
28. Welborn TA, Dhaliwal SS, Bennett SA. Waist-hip ratio is the dominant risk factor predicting cardiovascular death in Australia. *Med J Aust*. 179(11–12):580–585.
29. American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists & NAA for the S of O. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004;27(2):596–601.
30. Reckelhoff JF, Reckelhoff JF. Gender Differences in the Regulation of Blood Pressure. *Hypertenson*. 2001;37:1199–1208. doi:10.1161/01.HYP.37.5.1199.
31. Vassas TJ, Burghardt KJ, Ellingrod VL. Pharmacogenomics of sterol synthesis and statin use in schizophrenia subjects treated with antipsychotics. *Pharmacogenomics*. 2014;15(1):61–67. doi:10.2217/pgs.13.157.
32. Khatana SAM, Kane J, Taveira TH, Bauer MS, Wu W-C. Monitoring and Prevalence Rates of Metabolic Syndrome in Military Veterans with Serious Mental Illness. Mitchell AJ, ed. *PLoS One*. 2011;6(4):e19298. doi:10.1371/journal.pone.0019298.
33. Nasrallah HA, Meyer JM, Goff DC, et al. Low rates of treatment for hypertension, dyslipidemia and diabetes in schizophrenia: Data from the CATIE schizophrenia trial sample at baseline. *Schizophr Res*. 2006;86(1):15–22. doi:10.1016/j.schres.2006.06.026.

ORIGINAL RESEARCH

Key Words: amphetamine, opioid, benzodiazepine, anticholinergic, psychomotor vigilance task, reaction time, sustained attention, workplace safety

The Addition of Amphetamine to Potentially Sedating Medication Regimens: An Exploratory Investigation of the Impact upon Reaction Time and Sustained Attention

By James W. Price

ABSTRACT *~* ***Objectives****: The addition of amphetamine to a sedating medication may reduce sedation but does it augment reaction time and sustained attention for workers? The purpose of this exploratory study was gain insight into between group differences that would assist hypothesis formation for a subsequent hypothesis testing study.* ***Methods****: This study examined psychomotor vigilance task (PVT) performance for a group taking potentially sedating medications (opiates, benzodiazepines, anticholinergics, barbiturates or polypharmacy) while taking amphetamine to a group not taking amphetamine. Data was assessed using two-way between groups multivariate analysis of variance.* ***Results****: Multivariate testing found a ($p = .05$; $\eta 2 = .044$) difference in combined PVT measures between the amphetamine use groups. Tests of between-subjects effects established ($p = .006$; $\eta 2 = .042$) a difference in the number of minor lapses between the groups. Estimated marginal means of minor lapses revealed that the group taking amphetamine had 2.8 times the mean number of minor lapses than the group not taking amphetamine. A non-statistically significant trend was noted for the estimated marginal means of each sedating medication class and the use or nonuse of amphetamines that appears to correspond with the sedating medication's effect upon the cholinergic component of the attention system.* ***Conclusions****: Using PVT data, this exploratory study has provided information useful for generating the hypothesis that co-administration of an amphetamine with a sedating medication will result in arousal with a deficit of sustained attention related to the sedating medication's level of effect upon cholinergic activity.* Psychopharmacology Bulletin. *2017;47(2):22–35.*

Dr. James W. Price, D.O., M.P.H., Clinical Assistant Professor, Marian University College of Osteopathic Medicine, Cold Spring Road, Indianapolis, IN.

To whom correspondence should be addressed: Dr. James W. Price, D.O., M.P.H., Medical Director, St. Vincent Occupational Medicine Clinic, 2330 Lynch Road Evansville, Indiana 47711. Phone: 812-485-6900; Fax: 812-485-6909; E-mail: james.price@ascension.org

Introduction

Health care providers wrote 259 million prescriptions for opioids and opiates in 2012 and roughly 75 million benzodiazepine prescriptions in 2008.[1,2] The increasing reliance of Americans upon prescription medications for pain, anxiety and other maladies suggests that many are reporting to work with potentially sedating agents in their systems and these substances may be associated with work related accidents.[3–6] Stimulants are often co-administered with narcotics to mitigate sedation. Most research supporting this practice has been done in the palliative care setting, investigating pharmacologic treatment of overt sedation, but these studies fail to address cognitive function.[7–9] Additionally, none of the studies specifically referenced a working population.

Amphetamines have been used for cognitive and physical performance enhancement for nearly eight decades and are currently prescribed for several diagnoses, including narcolepsy, shift-work sleep disorder, appetite suppression and attention deficit hyperactivity disorder.[10–12] Functional magnetic resonance imaging and positron emission tomography have identified the prefrontal and anterior cingulate cortices as principal sites of actions for these agents.[13] It is in these areas that amphetamine increases extracellular norepinephrine and dopamine levels inducing arousal.[14,15]

Improvements in overall performance have been demonstrated after intake of amphetamines with sustain attention or tonic-alertness tasks appearing to be the most sensitive measures of the drug's effects.[16,17] Another study suggested that acute doses of amphetamine may also decrease several forms of impulsive behavior.[18] However, it was demonstrated shortly after the discovery of amphetamine sulfate that a dose of 10 mg by mouth is incapable of significantly improving performance of a monotonous skilled task unless this performance has been reduced by previously existing fatigue.[19] Users may perceive the drug as enhancing their cognition. However, objective measures indicate amphetamine has no more than small effects on cognition in healthy young adults and the effect may be related to their baseline dopaminergic tone.[20,21] While amphetamine provides a low-level enhancement of function, it also causes less conservative movement estimation, incorrect signaling, failing to stop at a red traffic lights, reduced reaction times and increased risk taking behavior that might be responsible for amphetamine-related road fatalities.[22–24]

The complexity of this topic makes hypothesis formation difficult. The addition of amphetamine may reduce sedation but does co-administration of amphetamine augment reaction time and sustained attention for workers taking potentially impairing prescription

medications? The answer to this question is very important in this era of over prescribing. Hypothesis generation is the first step towards pursuing a line of research that will provide clinically significant information that will ultimately be used to enhance workplace safety. The purpose of this exploratory study was to perform an uncontrolled retrospective assessment to gain insight into between group differences to assist hypothesis formation. A secondary aim was to ascertain any testing issues to be addressed in the design of a subsequent hypothesis testing study.

Methods

This study examined psychomotor vigilance task (PVT) performance for a group taking potentially sedating medications while taking prescribed dextroamphetamine, amphetamine or lisdexamfetamine to a group not taking an amphetamine. Optimal PVT performance depends on activation of the sustained attention system and the motor system to provide an objective measure of reaction time and sustained attention.[25] Sustained attention is the specific class of attention most closely related to the alertness systems, more precisely the tonic-alertness system.[17] Reaction time is the elapsed time between the presentation of a sensory stimulus and the subsequent behavioral response and it is dependent upon arrival of the stimulus at the sensory organ, conversion to a neural signal, neural transmission and processing, and muscular activation.[26] Both of these measures are fundamental to the performance of safety sensitive duties. Powell and colleges, using PVT testing, found that a group with a BrAC of .02 gm/210 L had an average mean reaction time of 263 ms and an average of .84 minor lapses. When the group's BrAC reached .08 gm/210 L the average mean reaction time increased to 276 ms and the number of minor lapses increased to 1.26.[27]

The population examined was males and females employed by a variety of industries from the confluence of Southern Indiana, Eastern Illinois and Western Kentucky that presented for pre-placement physical examinations or annual fitness-for-duty examinations. PVT testing was performed as an objective measure of sustained attention and reaction time per clinic protocol for any individual in a safety sensitive position taking a potentially impairing medication. Every physical examination completed from January 1, 2015 through December 31, 2015 that included PVT testing for potentially impairing medication use was chosen for this study. The electronic medical record (Systoc® 7.41) was searched and used for data collection. The age, gender, body mass index (BMI) and medications of each examinee were recorded along with the corresponding PVT results. The indication for amphetamine use varied

and was not recorded. The Institutional Review Board of St. Vincent Evansville Medical Center approved the study design and granted an inform consent waiver.

Psychomotor vigilance task testing was performed using PC-PVT© software.[28] Our system used a Fujitsu Lifebook T732™ with an Intel core™ i5 processor and 8 gigabytes of RAM running Windows 7 professional™ with a Razor™ Taipai gaming mouse. The PVT uses a 10 minute protocol, during which a millisecond counter is presented on the computer screen as the visual stimulus. The response is an immediate mouse button click. Each stimulus was delayed for a random period of between 2 and 10 seconds. A response during the delay was reported as a "false start". No response within 65 seconds of stimulus presentation was described as "no-response". A response between 500 ms and 1000 ms was described as a minor lapse and a response between 1000 ms and 65 seconds was described as a major lapse. The number of major lapses, minor lapses, and false starts, as well as the minimum reaction time, maximum reaction time, mean reaction time and median reaction time were reported at the end of each test session. Studies have suggested that physical fatigue is associated with an increased number of minor lapses (>500 msec) after controlling for age, BMI, depression and sleep apnea.[29] According to video data, lapses greater than 2669 ms were 95% likely to be eyes closed episodes (micro-sleep), while those 500–549 ms were 95% likely to be eyes open episodes (inattention) and reaction times of 1217 ms had an equal probability of being eyes open or closed episodes.[30]

Data analysis began with generation and exploration of descriptive statistics. Comparisons between amphetamine use and no amphetamine use group characteristics were performed using χ^2 tests for dichotomous variables and Mann-Whitney U test for continuous variables. Natural logarithmic transformation was performed on continuous dependent variables to mitigate the effects of non-normal distribution prior to further analysis. Statistical outliers were identified by calculation of Mahalanobis distances. Identified outliers were excluded from further analysis.[31] Two-way between groups multivariate analysis of variance (MANOVA) was accomplished with the independent variables being the type of impairing medication used by each subject and the status of amphetamine use. The type of impairing medication was categorized as prescribed use of opiates, benzodiazepines, anticholinergics, barbiturates or polypharmacy. The dependent variables were the natural logarithms of the seven PVT measures. Analysis suggested that three measures fit the model. These measures were the number of major lapses, the number of minor lapses, and the mean reaction time. Missing data was handled by pairwise exclusion.

Results

The study began with 199 cases. However, two cases were excluded for illicit drug use identified by urine drug testing, and 10 (5.1%) cases were excluded for being statistical outliers, leaving 187 valid cases. Concomitant amphetamine use was noted for 25 (13.4%) of the cases. Demographic, anthropometric and PVT measures stratified by stimulant use category are summarized in Tables 1 and 2. Of the 187 cases, 83 were men (44.4%) and 104 were women (55.6%). There appeared to be no significant difference in the distribution of the sexes between the amphetamine use groups. The mean age of subjects was 41.43 years with 24.1% being greater than 30 years, 48.1% between 30 years and 50 years and 27.8% greater than 50 years. There was a significant difference in the age make-up of the amphetamine use groups with the group using amphetamine being younger. The mean BMI was 31.21 kg/m^2; 20.3% having a BMI less than or equal to 25 kg/m^2, 25.7% being between 26 and 30 kg/m^2 and the remainder having a BMI greater than 30 kg/m^2. The group not using amphetamine had a significantly higher mean BMI than the group using an amphetamine. Most of the PVT assessments were performed because of polysubstance use (39.0%) or opiate use (32.1%), while the rest were performed for benzodiazepine (21.4%) or anticholinergic (7.5%) use. There were no individuals prescribed barbiturates. There appeared to be no difference in the sedating medication use patterns between the amphetamine use groups.

TABLE 1

Frequency Table for Demographic and Anthropometric Characteristics

		Using Amphetamine N = 25		Not Using Amphetamine N = 161		
Variable	Group	Frequency	Valid Percent	Frequency	Valid Percent	*P* Value (2-sided)
Sex	Male	8	32	75	46.6	*.251
	Female	17	68	86	53.4	
Impairing Medication	Opiate	6	24	54	33.5	.586
	Benzodiazepine	7	28	32	19.9	
	Anticholinergic	1	4	13	8.1	
	Polypharmacy	11	44	62	38.5	
Age (years)	<30 years	11	44	34	21.1	**.028**
	30–50 years	7	28	83	51.6	
	>50 years	7	28	44	27.3	
Body Mass Index (kg/m^2)	≤25	10	40	28	17.5	**.030**
	26–30	6	24	42	26.3	
	>30	9	36	90	56.3	

Notes: Chi-square test for independence ($\alpha = .05$). *Yates' correction for continuity.

TABLE 2

Descriptive Statistics for Continuous Variables Stratified by Amphetamine Use

VARIABLE	GROUP	N	MEAN (STANDARD DEVIATION)	SKEWNESS (STANDARD ERROR)	KURTOSIS (STANDARD ERROR)	*P VALUE (2-SIDED)
Age (years)	Taking Amphetamine	25	37.20 (14.33)	.13 (.46)	−1.57 (.90)	.097
	Not Taking Amphetamine	161	42.00 (11.66)	.06 (.19)	−.81 (.38)	
BMI (kg/m^2)	Taking Amphetamine	25	28.98 (7.98)	1.50 (.46)	2.99 (.90)	**.043**
	Not Taking Amphetamine	160	31.56 (7.02)	.51 (.19)	.22 (.38)	
Major lapses (>1000 ms)	Taking Amphetamine	25	.16 (.37)	1.97 (.46)	2.06 (.90)	.058
	Not Taking Amphetamine	161	.06 (.23)	3.90 (.19)	13.40 (.38)	
Minor lapses (500–1000 ms)	Taking Amphetamine	25	1.16 (1.49)	1.26 (.46)	.73 (.90)	.315
	Not Taking Amphetamine	160	.76 (1.06)	2.28 (.19)	8.37 (.38)	
False starts	Taking Amphetamine	25	3.40 (2.60)	.70 (.46)	−.11 (.90)	**.027**
	Not Taking Amphetamine	161	2.48 (3.15)	3.03 (.19)	12.33 (.38)	
Minimum reaction time (ms)	Taking Amphetamine	25	184.53 (18.04)	.29 (.46)	−.88 (.90)	.414
	Not Taking Amphetamine	161	188.88 (23.79)	.55 (.19)	.48 (.38)	
Maximum reaction time (ms)	Taking Amphetamine	25	723.08 (569.45)	2.33 (.46)	5.22 (.90)	.786
	Not Taking Amphetamine	160	606.42 (348.75)	3.58 (.19)	16.03 (.38)	
Mean reaction time (ms)	Taking Amphetamine	25	268.32 (39.76)	.65 (.46)	−.62 (.90)	.941
	Not Taking Amphetamine	161	263.76 (30.03)	.67 (.19)	.56 (.38)	
Median reaction time (ms)	Taking Amphetamine	25	253.88 (35.26)	.93 (.46)	.72 (.90)	.933
	Not Taking Amphetamine	161	252.24 (30.47)	.73 (.19)	.69 (.38)	

Note: *Mann-Whitney U test ($\alpha = .05$).

PVT measures were evaluated and violated the assumption of normal distribution (Table 2). These measures were transformed logarithmically for subsequent MANOVA testing. The data met the assumption of linearity and homogeneity of variance-covariance matrices. Multivariate testing (Table 3) found a 95% probability ($p = .05$) of a difference in combined PVT measures between the amphetamine groups with 4.4% ($\eta^2 = .044$) of the variance between the PVT measures explained by the amphetamine use of the subjects. No other statistically significant differences were found.

Levene's test was used to test the assumption of equality of variances. The assumption was not met for major lapses and mean reaction time. This finding was mitigated by using an alpha level of .025 for these variables during testing of between-subjects effects. The alpha level for minor lapses remained .05.

Tests of between-subjects effects examined how the independent variables affected each of the three PVT measures (Table 3). Bonferroni adjustment was performed on the alpha levels of each of the dependent variables to reduce the chance of type 1 error. The adjusted alpha level for major lapses and mean reaction time was .008 and the adjusted alpha level for minor lapses was .017. Comparison of the individual PVT measures with the amphetamine use groups established, with greater than 99% probability ($p = .006$), a difference in the number of minor lapses between the groups. 4.2% ($\eta^2 = .042$) of the variance in minor lapses between the groups is explained by amphetamine use. This was the only statistically significant difference discovered.

TABLE 3

Two-way Between Groups Multiple Analysis of Variance

MULTIVARIATE TESTS OF SIGNIFICANT DIFFERENCES AMONG THE GROUPS ON A LINEAR COMBINATION OF PVT MEASURES

EFFECT	PILLAI'S TRACE	F-VALUE	HYPOTHESIS DF	ERROR DF	SIG.[a]	PARTIAL ETA^2
Impairing Medication (A)	.069	1.385	9.0	531.0	.191	.023
Stimulant use (B)	.044	2.655	3.0	175.0	**.050**	.044[b]
A * B	.056	1.131	9.0	531.0	.339	.019

TESTS OF BETWEEN SUBJECTS EFFECTS

	MAJOR LAPSES[c]		MINOR LAPSES[d]		MEAN REACTION TIME[c]	
SOURCE OF VARIATION	F	SIG.	F	SIG.	F	SIG.
Impairing Medication (A)	.468	.705	1.822	.145	2.860	.038
Amphetamine use (B)	1.039	.309	7.695	**.006**[e]	2.585	.110
A * B	.088	.967	2.817	.041	1.164	.325

Notes: [a]$\alpha = .05$. [b]Consistent with a small to moderate effect-size. [c]$\alpha = .008$ after mitigating for violation of the assumption of equality of variance and subsequent Bonferroni adjustment. [d]$\alpha = .017$ after Bonferroni adjustment. [e]Partial Eta Squared = .042, small to moderate effect-size.

TABLE 4

Estimated Marginal Means for Between Subjects Effects Tests

Dependent Variable	Impairing Medication	Stimulant Use Group	Mean	Standard Error	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Major Lapses (>1000 ms)	Aggregate	Taking Amphetamine	.123	.076	−.027	2.73
		Not Taking Amphetamine	.042	.024	−.006	.090
	Opiates/Opioids	Taking Amphetamine	.167	.105	−.040	.373
		Not Taking Amphetamine	.037	.035	−.031	.106
	Benzodiazepines	Taking Amphetamine	.143	.097	−.048	.334
		Not Taking Amphetamine	.031	.045	−.058	.121
	Anticholinergics	Taking Amphetamine	0	.256	−.506	.506
		Not Taking Amphetamine	0	.071	−.140	.140
	Polypharmacy	Taking Amphetamine	.182	.077	.029	.334
		Not Taking Amphetamine	.098	.033	.034	.163
Minor Lapses (500–1000 ms)	Aggregate	Taking Amphetamine	2.007	.324	1.368	2.646
		Not Taking Amphetamine	.708	.103	.504	.912
	Opiates/Opioids	Taking Amphetamine	.933	.447	−.048	1.715
		Not Taking Amphetamine	.704	.149	.410	.997
	Benzodiazepines	Taking Amphetamine	1.286	.413	.470	2.102
		Not Taking Amphetamine	.594	.193	.212	.997
	Anticholinergics	Taking Amphetamine	5.000	1.094	2.841	7.159
		Not Taking Amphetamine	.615	.303	.017	1.214
	Polypharmacy	Taking Amphetamine	.909	.330	.258	1.560
		Not Taking Amphetamine	.918	.140	.642	1.194
Mean Reaction Time (ms)	Aggregate	Taking Amphetamine	281.756	8.900	264.192	299.321
		Not Taking Amphetamine	265.038	2.845	259.424	270.652

(*Continued*)

TABLE 4 (*Continued*)

DEPENDENT VARIABLE	IMPAIRING MEDICATION	STIMULANT USE GROUP	MEAN	STANDARD ERROR	95% CONFIDENCE INTERVAL LOWER BOUND	95% CONFIDENCE INTERVAL UPPER BOUND
	Opiates/Opioids	Taking Amphetamine	255.000	12.282	230.763	279.237
		Not Taking Amphetamine	252.889	4.094	244.810	260.968
	Benzodiazepines	Taking Amphetamine	273.571	11.371	251.132	296.011
		Not Taking Amphetamine	270.812	5.318	260.317	281.308
	Anticholinergics	Taking Amphetamine	332.000	30.084	272.631	391.369
		Not Taking Amphetamine	269.385	8.344	252.919	285.851
	Polypharmacy	Taking Amphetamine	266.455	9.071	248.554	284.355
		Not Taking Amphetamine	267.066	3.852	259.464	274.667

Inspection of estimated marginal means of minor lapses for the amphetamine use groups revealed that the group taking amphetamines had 2.8 times the mean number of minor lapses than the group not taking amphetamines (Table 4). A non-statistically significant trend was noted upon examination of the estimated marginal means for each impairing medication class and the use or nonuse of amphetamines. It appears that the group taking amphetamines had more minor lapses if they were taking anticholinergic medications (factor of 8.13), benzodiazepines (factor of 2.16) and opiate/opioids (factor of 1.32) than the corresponding groups not taking amphetamines (Table 4).

Discussion

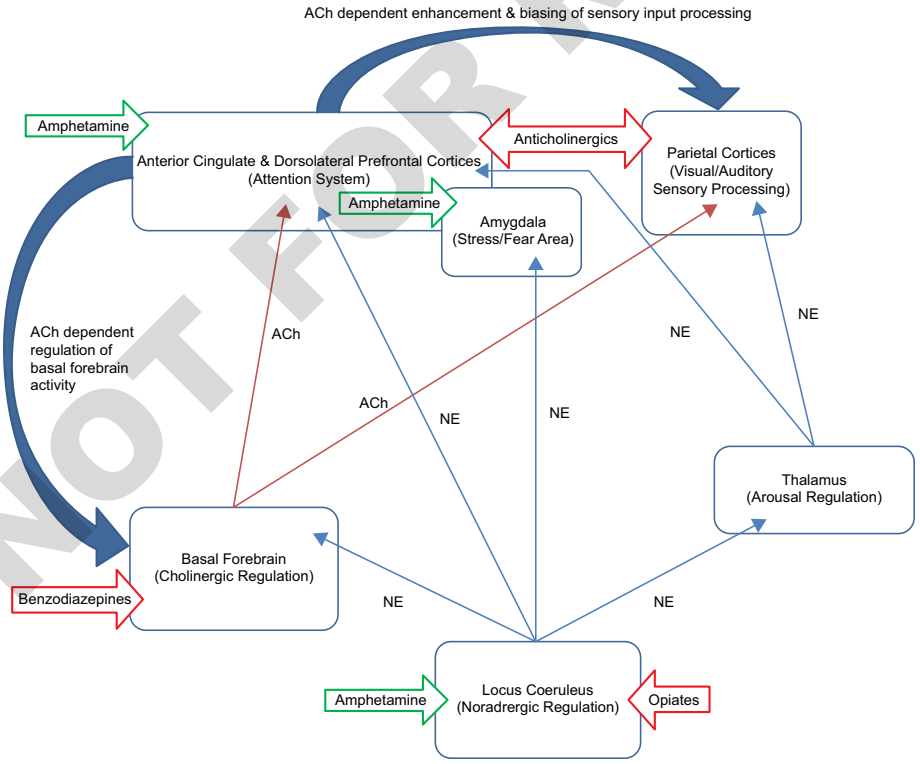
PVT performance is known to be sensitive to differences in sex, medication use, age and BMI[17,25]. The sex distribution and sedating medication use patterns were not meaningfully different between the studied groups and do not appear to be a source of bias in this investigation. There was a significant difference in age distribution between the amphetamine use and not-use groups, with the amphetamine use group being much younger than the not-use group. The BMI makeup of the two groups was also considerably dissimilar with the amphetamine use group having a lower mean BMI. The disparity of both of these variables should have biased the results towards better performance of the

amphetamine use group yet the group underperformed. This suggests that the actual difference between the amphetamine use and not-use groups may have been greater than reported.

The results suggest that individuals from the group taking amphetamine had significantly greater number of minor lapses consistent with impaired sustained attention. The estimated marginal means for between subjects' effects revealed a tendency toward more minor lapses for the anticholinergic medications, benzodiazepines and opiate/opioids groups if they were taking amphetamine. There is a plausible physiologic explanation for these findings (Figure 1). Attention processing of stimulating cues is largely mediated by norepinephrine release from neurons originating in the locus coeruleus and terminating in the basal forebrain prompting acetylcholine release.[32] Activation of the basal forebrain cholinergic projections is required for sustained attention performance. These projections stimulate the anterior

FIGURE 1

A Schematic Representation of The Sustained Attention System and its Relationship to Impairing Substances



Opiates, benzodiazepines and anticholinergic medications disrupt acetylcholine (Ach) dependent regulation of basal forebrain activity and sensory input processing. Co-administered amphetamine stimulates release and inhibits reuptake of norepinephrine (NE) and dopamine augmenting arousal, stress and fear but not attention.

cingulate, dorsolateral prefrontal and parietal cortices which modulate the function of the sensory regions by enhancing and biasing sensory input processing.[17] Norepinephrine release from neurons originating in the locus coeruleus terminating in the amygdala initiate stress or fear responses and neurons terminating in the thalamus result in arousal.[33] Different classes of medication upset this system by varying degrees with anticholinergic medications having the largest impact followed by benzodiazepines then opiates. Anticholinergic medications antagonize acetylcholine receptors in the attention and sensory areas, inhibiting acetylcholine dependent processes critical to sustained attention. Benzodiazepines produce GABA mediated attenuation of acetylcholine release disrupting acetylcholine dependent regulation of basal forebrain activity and sensory input processing. Opiates disrupt this system by suppressing norepinephrine release and subsequent acetylcholine release in the face of presenting stimuli. Amphetamines act by stimulating release and inhibiting reuptake of norepinephrine and dopamine augmenting arousal and contributing to stress and fear while lending little to bolster cholinergic dependent processes; the degree of which being dependent upon the mechanism inhibiting the cholinergic system.[34,35] Essentially, the addition of a stimulant to a potentially impairing medication may leave the individual aroused and stressed, with deficient sustained attention.

Based on the findings suggested by this study I hypothesize that the addition of amphetamine to a medication regiment that includes a sedating medication may result in arousal but will adversely affect sustained attention and possibly reaction time. The degree of the attention deficit will depend on the mechanism and degree of cholinergic impairment imparted by the sedating medication.

This study has several sources of systematic and random error. There is inherent selection bias in the design where subjects prescribed amphetamines for subjective complaints and objective deficits are likely to have poor PVT performance relative to a group not prescribed amphetamines. The PVT is sensitive to variations in sleep deprivation which may have also introduced error.[25] Random error may have been introduced based on the examinee's medication compliance, degree of motivation and level of stress.[25,17] These issues have little effect upon hypothesis formation, but will need to be controlled for in the design of a subsequent hypothesis testing study.

Summary

PVT performance has ecological validity in that it can reflect real-world risks. Deficits in sustained attention and timely reactions adversely

affect many safety sensitive duties, especially those in which work-pace or timely reactions are essential.[36] The findings suggest that many employed people have levels of sustained attention equal to or worse than people with BrAC concentrations of .08 gm/210 L. Using PVT data, this exploratory study has provided information useful for generating the hypothesis that co-administration of an amphetamine with a sedating medication will result in arousal, but with a sustained attention deficit which is dependent upon the mechanism of cholinergic impairment of the sedating medication.

There were several sources of systematic and random error which need to be addressed in the design of a subsequent hypothesis testing study. The design will require controlling for sleep deprivation, age, BMI, motivation and level of stress. Only stimulant naive subjects taking a stable dose of potentially sedating medication ought to be enrolled into the study. A third group that is not taking any potentially sedation or stimulating medications may also be added. We shall also consider adding a brief PVT practice session to assure understanding of proper test taking technique by examinees to mitigate random error presenting as statistical outliers.

This study was a first step toward providing clinically relevant data to be used for the improvement of workplace safety. As medical professionals we must be cognizant that each of our patients is part of a social system including the workforce. When therapies have the potential for causing cognitive impairment they not only put the patient at risk, but also put non-consenting third parties at risk. This study has provided useful information for hypothesis formation but it is clear that much work is to be done to test this hypothesis and provide actionable clinical recommendations. ✤

Acknowledgments

None

Conflict of Interest

There are no conflicts of interest or financial disclosures relevant to the topic of the submitted manuscript.

Disclosures

There are no outside sources of support to be identified. There have been no prior presentations of this manuscript.

References

1. Centers for Disease Control and Prevention. *Opioid Painkiller Prescribing: Where You Live Makes a Difference*. 2014; Accessed July 12, 2016.
2. Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. *JAMA Psychiatry*. 2015; 72(2):136–142.
3. Price J. Comparison of random and post-accident urine drug tests in southern Indiana coal miners. *Journal of Addiction Medicine*. 2012;6(4):253–257.
4. Price J. Benzodiazepines and workplace safety: an examination of urine drug tests. *Journal of Addiction Medicine*. 2014;8(5):333–337.
5. Price J. A comparison of random and post-accident urine opiate and opioid tests. *Journal of Addictive Diseases*. 2015;34(1):36–42.
6. Price J. The difference between random and post-accident urine drug test concentrations among Southern Indiana, Western Kentucky, and Eastern Illinois workers. *Journal of Addictive Medicine*. 2016; 10(6):414–417.
7. Webster L, Andrews M, Stoddard G. Modafinil treatment of opioid-induced sedation. *Pain Medicine*. 2003;4(2):135–140.
8. Bruera E, Brenneis C, Paterson A, MacDonald R. Use of methylphenidate as an adjuvant to narcotic analgesics in patients with advanced cancer. *Journal of Pain and Symptom Management*. 1989;4(1):3–6.
9. Yee J, Berde C. Dextroamphetamine or methylphenidate as adjuvants to opioid analgesia for adolescents with cancer. *Journal of Pain and Symptom Management*. 1994;9(2):122–125.
10. Molitch M, Eccles A. The effect of benzedrine sulfate on the intelligence scores of children. *American Journal of Psychiatry*. 1937;94(3):587–590.
11. Bradley C. The behavior of children receiving benzedrine. *American Journal of Psychiatry*. 1937;94(3):577–585.
12. Heal D, Smith S, Gosden J, Nutt D. Amphetamine, past and present–a pharmacological and clinical perspective. *Journal of Psychopharmacology*. 2013;27(6):479–496.
13. Pliszka S. Pharmacologic treatment of attention-deficit/hyperactivity disorder: efficacy, safety and mechanisms of action. *Neuropsychology Review*. 2007;17(1):61.
14. Berridge C, Stalnaker T. Relationship between low-dose amphetamine-induced arousal and extracellular norepinephrine and dopamine levels within prefrontal cortex. *Synapse*. 2002;46(3):140–149.
15. Boutrel B, Koob G. What keeps us awake: the neuropharmacology of stimulants and wakefulness-promoting medications? *Sleep*. 2004;27:1181–1194.
16. Koelega H. Stimulant drugs and vigilance performance: a review. *Psychopharmacology*. 1993;111(1):1–16.
17. Oken B, Salinsky M, Elsas S. Vigilance, alertness, or sustained attention: physiological basis and measurement. *Clinical Neurophysiology*. 2006;117(9):1885–1901.
18. de Wit H, Enggasser J, Richards J. Acute administration of d-amphetamine decreases impulsivity in healthy volunteers. *Neuropsychopharmacology*. 2002;27(5):813–825.
19. Newman H. The effect of amphetamine sulfate on performance of normal and fatigued subjects. *Journal of Pharmacology and Experimental Therapeutics*. 1947;89(2):106–108.
20. Ilieva I, Boland J, Farah M. Objective and subjective cognitive enhancing effects of mixed amphetamine salts in healthy people. *Neuropharmacology*. 2013;64:496–505.
21. Fleming K, Bigelow L, Weinberger D, Goldberg T. Neuropsychological effects of amphetamine may correlate with personality characteristics. *Psychopharmacology Bulletin*. 1995.
22. Silber B, Croft R, Papafotiou K, Stough C. The acute effects of d-amphetamine and methamphetamine on attention and psychomotor performance. *Psychopharmacology*. 2006;187(2):154–169.
23. Wardle M, Treadway M, Mayo L, Zald D, de Wit H. Amping up effort: effects of d-amphetamine on human effort-based decision-making. *The Journal of Neuroscience*. 2011;31(46):16597–16602.
24. Drummond S, Bischoff-Grethe A, Dinges D, Ayalon L, Mednick S, Meloy M. The neural basis of the psychomotor vigilance task. *Sleep*. 2005;28(9):1059.
25. Silber B, Papafotiou K, Croft R, Ogden E, Swann P, Stough C. The effects of dexamphetamine on simulated driving performance. *Psychopharmacology*. 2005;179(3):536–543.
26. Pain M, Hibbs A. Sprint starts and the minimum auditory reaction time. *Journal of Sports Sciences*. 2007;25(1):79–86.
27. Powell N, Riley R, Schechtman K, Blumen M, Dinges D, Guilleminault C. A comparative model: reaction time performance in sleep-disordered breathing versus alcohol-impaired controls. *The Laryngoscope*. 1999;109:1648–1654.
28. Khitrov M, Laxminarayan S, Thorsley D, Ramakrishnan S, Rajaraman S, Wesensten N, et al. PC-PVT: A platform for psychomotor vigilance task testing, analysis, and prediction. *Behavior Research Methods*. 2014;46(1):140–147.

29. Lee I, Bardwell W, Ancoli-Israel S, Dimsdale J. Number of lapses during the psychomotor vigilance task as an objective measure of fatigue. *J Clinical Sleep Medicine*. 2010;6(2):163–168.
30. Anderson C, Wales A, Horne J. PVT lapses differ according to eyes open, closed, or looking away. *Sleep*. 2010;33(2):197–204.
31. Stevens J. Outliers and influential data points in regression analysis. *Psychological Bulletin*. 1984;95(2):334.
32. Sarter M, Givens B, Bruno J. The cognitive neuroscience of sustained attention: where top-down meets bottom-up. *Brain Research Reviews*. 2001;35(2):146–160.
33. Ressler K, Nemeroff C. Role of norepinephrine in the pathophysiology of neuropsychiatric disorders. *CNS Spectrums*. 2001;6(08):663–670.
34. Rothman R, Baumann M, Dersch C, Romero D, Rice K, Carroll F, et al. Amphetamine-type central nervous system stimulants release norepinephrine more potently than they release dopamine and serotonin. *Synapse*. 2001;39(1):32–41.
35. Shoblock J, Maisonneuve I, Glick S. Differential interactions of desipramine with amphetamine and methamphetamine: evidence that amphetamine releases dopamine from noradrenergic neurons in the medial prefrontal cortex. *Neurochemical Research*. 2004;29(7):1437–1442.
36. Basner M, Dinges D. Maximizing sensitivity of the psychomotor vigilance test (PVT) to sleep loss. *Sleep*. 2011;34(5):581.

ORIGINAL RESEARCH

Key Words: depression, medication reconciliation, student pharmacist, treatment-resistant, medication history, ambulatory care, telephone, antidepressive agents

Impact of a Student Pharmacist Driven Medication Reconciliation and Antidepressant Treatment History Project at a Depression Clinic: A Pilot Study

By Stella S. Tang, Leanna Jaward, Kristen Ward, Sagar V. Parikh, Jolene R. Bostwick

ABSTRACT ~ Objectives: *To improve treatment of patients with depression, a new pilot service project involving student pharmacists who would conduct medication reconciliation and review of antidepressant treatment history was created and evaluated.* ***Experimental design:*** *A prospective study conducted at the University of Michigan Depression Center.* ***Principal observations:*** *From an initial sample of 78 referrals, 41 subjects were reached by phone, with 34 completing medication reconciliation and antidepressant treatment history. Of the 34 patients, 25 (73.5%) had at least one discrepancy identified in their medication list, resulting in 164 medication changes in the electronic medical record (EMR). A total of 105 past antidepressant trials were documented in the 34 individuals, with 34 (32.4%) trials found to be inadequate. Thirteen (38.2%) patients reported failure to respond to two different antidepressants from different classes. All 34 patients participated well in the phone calls and were willing to consult a pharmacist at their upcoming clinic visit.* ***Conclusions:*** *A student pharmacist pilot was feasible, identified many discrepancies in the medication record, and identified important medication treatment history in patients with depression in advance of the clinic visit. The project provides support for a specialized role for student pharmacists and demonstrates that interprofessional care can contribute to improved treatment of depression.*
Psychopharmacology Bulletin. *2017;47(2):36–41.*

Medication reconciliation is a key part of medication therapy management that involves evaluating a patient's medication regimen for medication errors and comparing existing and previous medication regimens.[1] The American Pharmacists Association (APhA) and the American Society of Health-System Pharmacists (ASHP) have

Ms. Tang, BS, PharmD Candidate, Ms. Jaward, PharmD Candidate, Drs. Ward, PharmD, Bostwick, PharmD, BCPS, BCPP, University of Michigan College of Pharmacy, Ann Arbor, MI; Dr. Parikh, MD, Department of Psychiatry, Michigan Medicine. The first two authors contributed equally to this work.

To whom correspondence should be addressed: Dr. Jolene R. Bostwick, PharmD, BCPS, BCPP, Associate Chair, Department of Clinical Pharmacy and Clinical Pharmacist, Michigan Medicine, 428 Church Street, Ann Arbor, MI 48109-1065. Phone: (734)764-0810; Fax: (734)763-4480; E-mail: jkingsbu@med.umich.edu

established the goal of medication reconciliation as "to obtain and maintain accurate and complete medication information for a patient and use this information within and across the continuum of care to ensure safe and effective medication use."[1] Medication reconciliation reduces medication errors in prescribing, assures safe medication use by patients, and facilitates appropriate monitoring and adjustment of drug therapy.[1]

Several studies that assessed the impact of pharmacy driven medication reconciliation programs in various settings found pharmacy personnel, including technicians, student pharmacists, and pharmacists, were able to identify discrepancies in up to 88% of patients studied.[2–4] Such discrepancies can be clinically significant, with one study identifying 17.1% of discrepancies as serious or potentially life-threatening.[4]

To the best of our knowledge, a similar study has not been conducted in an outpatient depression clinic setting. In this setting, medication reconciliation is particularly important. The STAR*D trial demonstrated only 36.8% of patients achieved remission after initial treatment for depression, so most patients required many additional medication trials.[5,6] Individuals presenting to depression clinics frequently have histories of multiple medication trials without good documentation, making psychiatric evaluation more challenging. To improve care, interprofessional approaches such as having pharmacists clarify medication treatment history can contribute to effective clinic evaluation and treatment. We report here a pilot study exploring implementation, feasibility, and outcomes of a medication reconciliation and antidepressant treatment history program led by a pharmacy team including student pharmacists in a large, Midwestern academic setting.

Methods

The study received an exempt, not regulated status, from the University of Michigan Institutional Review Board. A team of five student pharmacists and two pharmacist preceptors practicing in psychiatry conducted this pilot over a 12-week period beginning on February 18, 2016 and ending on May 12, 2016. All individuals scheduled for an initial referral at the University of Michigan Depression Clinic were contacted to participate in a pharmacy telephone encounter approximately one week prior to the clinic visit. During the first part of the telephone call, students requested a list of current medications, including: (1) all prescription products, including both psychiatric and non-psychiatric medications, (2) non-prescription products, including over-the-counter medications, vitamins, herbals, and supplements. The second part of the telephone call documented past antidepressant trials as well as adjunctive therapies, with details on dose, duration of therapy, side

effects experienced, response to therapy, and reason for discontinuation. Finally, students encouraged patients to share any concerns and also asked whether they would be willing to discuss their medications with a pharmacist if a medication change was made at the clinic visit. The length of telephone calls was recorded.

Students used the duration of therapy information to classify antidepressant trials as adequate (trial length of at least two months) or inadequate, and whether criteria for treatment-resistant depression (TRD) were met (failure to respond to two adequate trials of two different classes of antidepressants).[7] A drug interaction screen was also performed. Information gathered from the calls were documented in a clinic note in the electronic medical record (EMR).

Results

Data were analyzed using descriptive statistics. Of the 78 patients attempted, 41 (52.6%) were reached by telephone and 34 (43.6%) successfully completed the pharmacy encounter. Of these 34 patients, 24 (70.6%) were women and patients had an average age of 40.7 years (range 17 to 69 years). Seven patients who declined the service cited reasons as inconvenient timing (57.1%, n = 4), clinic appointment cancellation (28.6%, n = 2), and preference for reviewing medications with a clinician (14.3%, n = 1). Call durations for the 34 patients who successfully completed the pharmacy encounter ranged from 5 to 50 minutes, and the average call length was 18.4 minutes.

In the patient population (n = 34), a total of 76 psychiatric medications were being taken, with an average of 2.2 medications per patient. The total number of medication changes made in the EMR was 164 (Table 1), with an average of 4.8 changes per patient. A total of 25 (73.5%) patients had at least one discrepancy identified in their medication list. Over the course of the project, 31 potentially clinically

TABLE 1

Medication Changes Made % (n)

	TOTAL NUMBER OF DELETIONS	TOTAL NUMBER OF ADDITIONS	TOTAL NUMBER OF DOSE CHANGES
Prescription medications (n = 109)	93.1 (27)	57.6 (72)	100.0 (10)
Nonprescription medications (n = 9)	3.4 (1)	6.4 (8)	0.0 (0)
Vitamins/herbals/supplements (n = 46)	3.4 (1)	36.0 (45)	0.0 (0)
Total	100 (29)	100 (125)	100 (10)

TABLE 2

Description of Antidepressant Treatment Histories % (n)

	TOTAL NUMBER OF PATIENTS WHO TRIED EACH CLASS	TOTAL NUMBER OF PATIENTS WITH AN ADEQUATE TRIAL[a]	TOTAL NUMBER OF PATIENTS REPORTING IMPROVED SYMPTOMS	TOTAL NUMBER OF PATIENTS WHO EXPERIENCED SIDE EFFECTS
SSRI	61.8 (21)	85.7 (18)	52.4 (11)	47.6 (10)
SNRI	47.1 (16)	62.5 (10)	12.5 (2)	31.3 (5)
TCA	11.8 (4)	100 (4)	25 (1)	75 (3)
MAOI	8.8 (3)	66.7 (2)	33.3 (1)	100 (3)
Other	47.1 (16)	75 (12)	31.3 (5)	31.3 (5)

Note: [a]Defined as a length of at least 2 months.
Abbreviations: MAOI, monoamine oxidase inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

significant drug-drug interactions were identified. A total of 18 (52.9%) patients had at least one drug-drug interaction in their current medication list. Patient-reported medication lists included between 0 and 5 drug-drug interactions.

Seventeen (50.0%) patients shared the following medication concerns: side effects from current medications (35.3%, n = 6), financial issues (35.3%, n = 6), decreased effectiveness of current medications (35.3%, n = 6), persistent depression symptoms (23.5%, n = 4), and adherence difficulties (11.8%, n = 2). Further, one (5.9%) patient each identified the following: lack of understanding about medications, incorrect diagnosis, and lack of access to psychiatric services.

A total of 105 antidepressant medications were tried by the surveyed population, with an average of 3.1 past medication trials per patient. Nearly one-third (32.4%) of antidepressant medication trials were considered inadequate trials (Table 2). Of the 105 past antidepressant medication trials with documented reasons for discontinuation, the most common reason was attributed to no improvement in mood symptoms (45.7%, n = 48), with the second most common reason being medication side effects (28.6%, n = 30). A total of 13 patients (38.2%) were considered to have TRD.

Of the 34 patients who completed the pharmacy encounter, all (100.0%) reported they would be willing to discuss their medications and associated side effects with a pharmacist if a medication change was made at the clinic visit.

Limitations

The students attempted to contact 78 patients and reached only 52.6% of those patients. Additionally, of the seven patients who declined the

service, 57.1% cited their reason as inconvenient timing. An additional limitation is the lack of external health records to validate the history of medication use and response.

Conclusions

The student pharmacist driven pilot project proved to be valuable. The pharmacy team identified patient-reported discrepancies in 73.5% of patients reached by telephone. This result is similar to those of previous studies involving student pharmacists.[2,3] The record of treatment failure was also a valuable contribution to the patient record and was of assistance to psychiatrists evaluating the patients. These findings highlight the positive impact of a medication reconciliation service in an outpatient depression clinic setting and demonstrates a role for interprofessional care. Further evaluation is necessary to establish the clinical impact of identification of such discrepancies.

In addition, the student pharmacist-patient interactions disclosed patient concerns that may be addressed by pharmacy intervention. For example, of the 17 patients who voiced concerns, 35.3% revealed that they had difficulty paying for their medications. A pharmacy team may refer such patients to patient assistance programs or recommend more cost-effective alternatives to clinicians. Additionally, the findings of the pilot project showed 32.4% of antidepressant medication trials were inadequate, and the most common reason for discontinuing antidepressant medications was no improvement in mood symptoms. These results signify an opportunity for pharmacists to provide patient education, specifically to provide support and reinforce onset of action of antidepressant medications. All patients surveyed were willing to engage with a pharmacist regarding their medications, which suggests that this is an appropriate future direction to explore within the clinic.

The pilot confirmed student pharmacists are well-suited for providing the service. Additional considerations include that this service may be integrated into the required Introductory Pharmacy Practice Experiences (IPPE) after students complete required training. Such training would include an orientation to the EMR system, as well as a review of the telephone call script and mock interactions with a pharmacist preceptor and/or psychiatrist.The results of the pilot project support the need for pharmacy services in an outpatient depression clinic setting. Student pharmacists can lead this type of service with the oversight of pharmacist preceptors.

Disclosures

Dr. Parikh serves as a consultant to Takeda, has a research contract with Assurex, and is a shareholder in Mensante. Ms. Tang, Ms. Jaward, Dr. Ward, and Dr. Bostwick have no conflicts of interest to report.

References

1. American Pharmacists Association; American Society of Health-System Pharmacists; Steeb D, Webster L. Improving care transitions: optimizing medication reconciliation. *J Am Pharm Assoc*. 2012;52(4):e43–e52.
2. Ashjian E, Salamin LB, Eschenburg K, Kraft S, Mackler E. Evaluation of outpatient medication reconciliation involving student pharmacists at a comprehensive cancer center. *J Am Pharm Assoc*. 2015;55(5):540–545.
3. Procopio GL, Faley B, Wynd MA, Finefrock D, Kobayashi M, Feldman J. Pharmacy collected medication histories in an observation unit. *SAGE Open Med*. 2015;3:2050312115598872.
4. Wills BM, Darko W, Seabury R, Probst LA, Miller CD, Cwikla GM. Pharmacy impact on medication reconciliation in the medical intensive care unit. *J Res Pharm Pract*. 2016;5(2):142–145.
5. Little A. Treatment-resistant depression. *Am Fam Physician*. 2009;80(2):167–172.
6. Howland RH. Sequenced treatment alternatives to relieve depression (STAR*D): Part 2: Study outcomes. *J Psychosoc Nurs Ment Health Serv*. 2008;46(10):21–24.
7. Souery D, Amsterdam J, de Montigny C, Lecrubier Y, Montgomery S, Lipp O, et al. Treatment resistant depression: methodological overview and operational criteria. *Eur Neuropsychopharmacol*. 1999;9(1–2):83–91.

Key Words: schizophrenia, psychopharmacology, antipsychotic medication, long-acting injectable antipsychotics; paliperidone palmitate

Long-Acting Injectable Paliperidone Palmitate: A Review of Efficacy and Safety

By Matthew T. Morris, Sandip P. Tarpada

ABSTRACT ~ ***Objective:*** *Summarize and synthesize the current literature regarding long-acting injectable paliperidone palmitate for the treatment of schizophrenia.* ***Methods:*** *A literature search of PubMed, Embase, and Web of Science was conducted in February 2016, using the following search terms in varying permutations: schizophrenia; antipsychotic medication; long-acting injectable; paliperidone palmitate; 3-monthly injectable.* ***Results:*** *Once-monthly injectable paliperidone palmitate (PDP) has demonstrated comparable efficacy as 1st-generation long-acting injectable antipsychotics (LAIAs) in reducing disease severity and re-hospitalizations in schizophrenic patients. However, PDP leads to significantly less extrapyramidal symptoms than these older medications indicating a superior safety profile. Compared to oral 2nd-generation antipsychotics, PDP has shown less incidence of disease relapse related to medication non-compliance, particularly in real world populations. It also showed a similar safety profile as oral 2nd-generation antipsychotics, but with greater incidence of mild injection-site pain. A novel 3-monthly formulation of PDP has shown similar safety and efficacy as once-monthly PDP compared to placebo.* ***Conclusions:*** *Overall, both 1-month and 3-month formulations of PDP are safe and effective in the treatment of schizophrenia and schizoaffective disorder. They may be most effective in patients with prior failed treatment of oral antipsychotics or other LAIAs, in patients with a history of medication noncompliance, or in patients with an individual preference for less frequent dosing.* Psychopharmacology Bulletin. *2017;47(2):42–52.*

Introduction

Schizophrenia is a chronic mental disorder characterized by deficiencies in thought processes, perceptions, and emotions. This disorder is relatively common, affecting roughly 1.1% of the US adult population, more often in men than in women.[1,2] It can also be severely disabling, making it difficult for those affected to hold jobs, form relationships, and even attend to their activities of daily living. Schizophrenia typically presents in early adulthood and follows a chronic course throughout the patient's life, significantly affecting quality of life and ultimately leading to an average 10-year reduction in life expectancy.[3] Due to the prevalence

Drs. Morris, BA, Tarpada, BA, Albert Einstein College of Medicine, Bronx, NY, USA.

To whom correspondence should be addressed: Dr. Matthew T. Morris, BA, 1935 Eastchester Rd, Apt. 23A, Bronx, NY 10461, United States. Phone: (949) 554-4632; E-mail: mtmorris@mail.einstein.yu.edu

and severity of this disease, it remains one of the most burdensome and devastating illnesses in the world today.[4] Nonetheless, the development of novel pharmacological treatments has dramatically improved our ability to manage this disease.

The advent of antipsychotic medication in the mid-20th century has allowed for good control of positive symptoms of schizophrenia, eliminating or reducing them to a tolerable level in up to 70% of patients.[5,6] Maintenance treatment with antipsychotics is recommended indefinitely, even for those who have achieved remission following a first psychotic break. Furthermore, oral formulations of these drugs allowed this treatment to take place in the outpatient setting, thereby reducing the burden of disease on the patient. However, this first generation of antipsychotics carry considerable side effects, most notably extrapyramidal symptoms (EPS), including akathisia, pseudoparkinsonism, and dystonia. These motor symptoms have been shown to be dose-dependent, occurring with greater frequency and severity at higher doses.[7] Due in part to a combination of poor side effect profiles and patient cognitive dysfunction, noncompliance with these drugs is very common.[8] Newer medications, collectively termed 2nd-geneneration ("atypical") antipsychotics were able to achieve similar suppression of positive symptoms while reducing the incidence and severity of EPS.[9,10] However, despite improved side-effect profiles, noncompliance continues to be an issue with 2nd-generation antipsychotics. In fact, compliance with oral maintenance therapy for schizophrenia is estimated at merely 40%–60% 1-year after discharge from an acute episode.[7,11]

Long Acting Injectable Antipsychotic (LAIA) Medication

Noncompliance with maintenance treatment in schizophrenic patients is associated with greater rates of disease relapse.[12] Disease relapse often leads to re-hospitalization, creating potentially immense cost and burden to the patient and their family, as well as poorer long-term outcomes.[12,13] Long-acting injectable antipsychotics (LAIAs) were created largely to address the issue of noncompliance by allowing the medication to be administered only once every 2–4 weeks rather than each day. Also referred to as "depot" injections, these medications are administered via gluteal or deltoid IM injection. In general, LAIAs result in more stable serum levels of the drug and fewer dose-related side effects compared to oral medication. For example, Ereshefsky et al compared pharmacodynamics and pharmacokinetics between comparably bioavailable doses of oral and LAI risperidone. The authors found that, compared to oral risperidone, LAI risperidone showed closer correlation between administered dose and serum levels,

resulting in more precise dosing and less difference between peak and trough serum drug levels.[7] There is a direct relationship between serum drug levels and EPS, so by reducing peak serum levels, LAIAs can theoretically reduce the occurrence of these side effects, although clinical studies have shown mixed results.[14–16]

Several studies have shown the efficacy of these drugs in improving outcomes in schizophrenia compared to placebo control. For example, in a double-blind RCT of 403 patients who had achieved good stabilization of acute schizophrenia, Kane et al administered either aripiprazole-IM-depot injection or placebo every 4 weeks for 1 year. They observed significantly greater improvement in the Positive and Negative Syndrome Scale (PANSS) and lower rates of impending relapse with aripiprazole than with placebo, indicating that LAI aripiprazole is a safe and effective alternative to oral aripiprazole.[17] Furthermore, other studies have compared LAIAs to their oral equivalent to better establish the case for their use. Chue et al randomized 640 patients with well-controlled schizophrenia to receive either LAI or oral risperidone for 12 weeks, finding similar improvement in PANSS between groups and no reported adverse events.[15] In a case series of 38 chronically psychotic, hospitalized patients previously receiving oral haloperidol, Deberdt et al injected haloperidol decanoate every 4 weeks at varying doses. They found that LAI haloperidol resulted in equally effective control of psychotic symptoms and no increase in EPS or injection-site pain compared to daily oral administration.[16] These results suggest comparable efficacy and safety between LAI and oral antipsychotics.

Despite intuitive assumptions that LAIAs can lead to superior compliance rates compared to oral antipsychotics in schizophrenic patients, several studies have found no difference in compliance rates between treatment modalities. For example, Rosenheck et al randomized 369 VA patients with unstable schizophrenia to receive either LAI risperidone or an oral antipsychotic. They found no significant difference between groups in terms of re-hospitalization, reported compliance, psychiatric symptoms, quality of life, and neurological side effects, but patients receiving LAI risperidone reported more injection-site pain and EPS than those receiving oral medication.[14] In addition, a 2005 meta-analysis of 6 RCTs comparing LAI fluphenazine to oral antipsychotics found no reduction in relapse with injectable medication.[18] However, some have argued that these results can be confounded by highly compliant study populations that are not representative of the general schizophrenic population. Addressing this source of bias, a claims-based analysis by Marcus et al compared compliance and re-hospitalization rates in Medicaid

patients with recent history of noncompliance who were recently hospitalized for schizophrenia and prescribed either oral or LAI antipsychotics upon discharge. The authors found that LAIAs led to lower rates of both noncompliance and re-hospitalization than oral medication, but that this difference was only significant with 2nd-generation LAIAs.[19] Several other studies have come to similar conclusions, finding improved compliance and long-term outcomes in patients prescribed LAIAs than in patients prescribed oral antipsychotics.[31,39] Overall, research has demonstrated that LAIAs, particularly 2nd-generation, are as safe and effective for maintenance treatment of schizophrenia as oral antipsychotics, suggesting that compliance can potentially be improved without sacrificing medication efficacy.[14–17,20]

Paliperidone Palmitate

Paliperidone palmitate (PDP) is a LAI formulation of the atypical antipsychotic paliperidone, the primary active metabolite of risperidone. It was approved by the FDA for acute and maintenance therapy of schizophrenia and schizoaffective disorder in 2009. This drug is a palmitate ester of paliperidone, prepared in an aqueous suspension of nanocrystals equipped with a sustained-release mechanism, resulting in slow dissolution in vivo. These nanocrystals are roughly 10 times smaller than the particles that one would find in a standard drug powder, creating substantially increased drug-solution surface area. Therefore, the drug solution is both able to more rapidly achieve steady state and maintain this steady state for a longer period of time than other LAIAs.[21,22] Effects of the drug are usually seen roughly 8 days following injection, and peak plasma level is reached roughly 13 days after injection. Serum half-life is roughly 25–49 days, and standard dosing schedule is induction therapy with 2 injections one week apart, followed by maintenance dose every 4 weeks.[23,24]

PDP in Acute-Phase Therapy

PDP injection has proven to be effective in improving psychotic symptoms in both acute and maintenance phases of schizophrenia. In a double-blind RCT of 652 patients with acutely exacerbated schizophrenia, Pandina et al administered either PDP 150 mg or placebo injection on day 1, followed by a set dose of PDP on placebo on day 8 and monthly thereafter.[25] They found significantly greater improvement in PANSS with PDP over placebo, and sufficient serum levels of drug to exert effects by day 8. The most common side effects they observed in

the PDP group were injection-site pain (7.6%), dizziness (2.5%), and sedation (2.3%).[25] Several other studies were performed with similar designs, and unanimously observed that monthly PDP injections significantly improved PANSS outcomes over placebo.[26–28] The PDP groups generally experienced higher rates of headache, nausea, and extremity pain than placebo, as well as slightly elevated BMI and weight in a dose-dependent fashion. Some studies reported higher levels of patient-evaluated injection-site pain with PDP injection, but others reported no difference. There was generally no difference observed between PDP and placebo groups in terms of extrapyramidal symptoms, although parkinsonism was the most commonly occurring movement disorder in the treatment groups. Overall, numerous double-blind RCTs of LAI PDP are in agreement that it constitutes a safe and effective treatment for acutely exacerbated schizophrenia with relatively few side effects.[23,25–28]

PDP in Maintenance-Phase Therapy

PDP injection has also been demonstrated to be effective in maintenance therapy for schizophrenia. Hough et al transitioned 410 patients with schizophrenia from previous oral antipsychotic to PDP injection therapy, stabilized them on PDP maintenance therapy, and subsequently randomized them to either continue receiving PDP or switch to placebo for the remainder of the study.[29] They found that a majority of patients in the placebo group experienced disease relapse, with a median time-to-relapse of 163 days, while less than 25% of patients in the PDP group relapsed. Mean PANSS outcomes were similar between groups at baseline, but at 40 weeks were significantly lower in the PDP group. There was no difference between groups with respect to adverse events, but the PDP group experienced a mean 1.9 kg weight-gain while the placebo group experienced none.[29] Moreover, many patients in which LAI therapy is indicated have experienced persistent symptoms despite oral antipsychotic medications. In a double-blind RCT, Silwa et al evaluated the use of monthly PDP injections versus placebo in schizophrenic patients who remained symptomatic after a trial of oral risperidone therapy.[30] They found that PDP significantly improved PANSS, global illness ratings, and functional outcomes over placebo. The most commonly observed adverse events were insomnia, anxiety, and headache. Similar to its primary use in acute-phase schizophrenia, use of PDP in maintenance-phase and persistent schizophrenia has been shown to yield positive outcomes, with the most consistently observed adverse effects being weight gain and insomnia.[30]

PDP in Relation to Oral Antipsychotics

In comparison with oral antipsychotic medications, LAI PDP therapy has shown positive results, both in terms of efficacy and safety. Alphs et al investigated PDP therapy in a "real world" schizophrenic population, defined as those with complicated disease, a history of incarceration, and previous oral antipsychotic use.[31] They designated these patients to receive open-label treatment with either LAI paliperidone or one of seven different daily oral antipsychotics. No differences were seen between groups in terms of social functioning or severity of illness, but medication compliance was higher and treatment failure rate was significantly lower with PDP than with oral medication. In terms of adverse events, only injection-site pain was seen more frequently in the PDP group.[31] These results support previous findings that disease relapse is associated with medication noncompliance, and suggest that PDP may be a particularly suitable treatment option for patients with a high likelihood of noncompliance.[31] In their previously mentioned Medicaid claims-based study, Marcus et al observed a lower rate of rehospitalization in patients receiving PDP than in those receiving any other available drug formulation, further supporting its efficacy at maintaining disease remission.[19] Furthermore, many patients initiated on PDP therapy are transitioned from 2nd-generation oral antipsychotics, and must be instructed when to discontinue their previous medication to avoid both over-dosing and gaps in therapy. Doshi et al examined current approach to this issue in an observational claims-based study by looking for simultaneous prescription of LAI and oral antipsychotics in recently-discharged schizophrenic patients.[32] They found that, of all available LAIAs, PDP was least frequently prescribed with an oral antipsychotic, likely due to its fast-achievement of steady-state and subsequent therapeutic effect. However, they note that when co-prescription occurred, in a majority of instances it overlapped substantially with time therapeutically covered by the LAI medication.[32] These results suggest that some degree of over-dosing exists during the transition from oral to LAI antipsychotic therapy following hospitalization for acute exacerbation of schizophrenia. However, more research must be done to determine the clinical consequences of such over-dosing, and ultimately to determine an optimal transition-dosing schedule based on clinical evidence.

PDP in Relation to Other LAIAs

While PDP therapy appears superior to placebo and at least non-inferior to oral antipsychotics, we still must determine its relative safety

and efficacy compared to other available LAIAs to make recommendations regarding its use. Gopal et al conducted a meta-analysis of RCTs investigating LAIAs versus placebo to calculate relative number-needed-to-treat (NNT) and number-needed-to-harm (NNH) for these medications.[33] In the acute phase of schizophrenia, they found NNT to be 6, defined as a 30% improvement in PANSS, and found NNT in maintenance phase to be 2, defined as prevention of relapse for 12 months. These values were similar to those calculated for first-generation LAIAs, such as haloperidol-decanoate (HPD), indicating similar efficacy. In terms of developing movement disorders, such as akathisia, tremor, and tardive dyskinesia, NNH varied considerably, but was significantly higher with PDP than with first-generation drugs. These same results were observed with regard to anticholinergic use, indicating a lower propensity for movement disorders to occur with PDP injections.[33] McEvoy et al corroborated these findings in a double-blind RCT comparing PDP to HPD injections in schizophrenic patients deemed to be at risk of relapse, and therefore good candidates for LAIA use. They observed similar rates of efficacy failure with PDP (33.8%) as with HPD (32.4%), but observed greater weight gain (+2.17 vs −0.96 kg) and serum prolactin levels with PDP and greater rates of akathisia with HPD.[9] Furthermore, although primary clinical research comparing PDP to other 2nd-generation LAIAs is lacking, Einarson et al conducted a cost-effectiveness analysis of PDP, LAI risperidone, and LAI olanzapine in acute and maintenance schizophrenia.[34] In their analysis, they conclude that PDP exhibits superior clinical outcomes, determined using Quality-Adjusted Life-Years, days in remission, hospital re-admissions, and emergency room visits as outcomes measures. They also found that PDP costs significantly less overall when the aforementioned clinical factors are taken into account, resulting in the conclusion that PDP is more cost effective than either LAI 2nd-generation antipsychotic.[34] However, to make a recommendation regarding their relative safety and efficacy, further research must directly compare their clinical use.

Paliperidone Palmitate 3-Monthly Injections

Paliperidone palmitate 3-monthly injectable (PDP3M) is a novel formulation of IM injectable paliperidone palmitate with a significantly longer half-life than the once-monthly formulation. It was approved by the FDA in 2015 for use in schizophrenia and schizoaffective disorders. Ravenstjin et al completed a phase 1 pharmacokinetics study of the novel drug, finding that peak serum concentration was reached at 23–34 days post-injection, and half-life *in vivo* was roughly 2–4 months.[35] Of note,

while the half-life of PDP is equivalent between gluteal and deltoid injection sites, the half-life of PDP3M is slightly greater with gluteal injection. The most commonly occurring adverse events that they noted were headache and nasopharyngitis, followed by weight-gain and back pain. Due to the extremely long half-life of PDP3M, it is recommended to only begin treatment in patients who have received at least 4 months of PDP, in order to assess individual tolerability.[36] When switching these patients from PDP to PDP3M, it is important to give the first dose of PDP3M at the time of their next scheduled dose of PDP, and to initiate treatment with a dose 3.5 times greater than scheduled dose.[36] Following that induction dose, a regular maintenance dosing schedule of one injection every 3 months should be followed.[36]

Berwaerts et al evaluated the clinical safety and efficacy of this drug in a double-bind RCT comparing the use of PDP3M to placebo in patients diagnosed with schizophrenia.[37] They initially administered monthly injections of PDP during a 17-week transition phase, subsequently administered 1 dose of PDP3M in a 12-week maintenance phase, and finally randomized patients to receive a fixed dose of PDP3M or placebo for the remainder of the study. The authors observed significantly greater rates of disease relapse with placebo than with PDP3P, supporting its efficacy in maintaining remission in schizophrenia. In terms of treatment-emergent adverse events, the PDP3M group experienced greater incidence of headache (9%), weight gain (9%), nasopharyngitis (6%), and akathisia (4%) than the control group.[37] In a phase 3 non-inferiority study, Savitz et al stabilized 1,016 schizophrenic patients on monthly PDP injections for 17 weeks, and subsequently randomized these patients to either switch to PDP3M or continue receiving PDP injections.[38] The authors observed similar disease relapse rates and clinical measures of disease severity between groups. They also observed similar safety/tolerability profiles between groups, with the most common treatment-emergent adverse event being weight gain, experienced by 21% of patients in each group.[38] Therefore, PDP3M has demonstrated equal safety and efficacy as PDP, and may be preferable to select patients due to less frequent dosing schedule.

Conclusions

Schizophrenia is an incredibly devastating and relatively common disease, but advancements in antipsychotic medication has proved to dramatically lessen the burden of this disease. However, due to cognitive and judicial compromise of those who suffer from it, medication non-compliance commonly leads to poorer outcomes for patients. Compared to oral antipsychotics, LAIAs have been shown to improve compliance

and lead to lower disease relapse and re-hospitalization rates in real-world populations. PDP, a once-monthly LAIA, has demonstrated good efficacy in reducing disease severity and re-hospitalizations in schizophrenic patients, with a similar safety profile as many 2nd-generation oral antipsychotics. PDP exhibits similar efficacy as 1st-generation LAIAs, such as haloperidol-decanoate, but is associated with significantly less EPS and greater metabolic effects. PDP3M, a once-three-monthly LAIA, is a recently-approved formulation of paliperidone palmitate that exhibits similar efficacy and safety as PDP in preliminary trials. Overall, both 1-month and 3-month formulations of PDP are safe and effective in the treatment of schizophrenia and schizoaffective disorder. They may be most effective in patients with prior failed treatment of oral antipsychotics or other LAIAs, in patients with a history of medication noncompliance, or in patients with an individual preference for less frequent dosing. However, further research directly comparing both PDP formulations to other 2nd-generation LAIAs to make a definitive recommendation. ✤

Disclosures of Potential Conflicts of Interest

On behalf of both authors, the corresponding author states that there are no conflicts of interest or sources of funding to declare.

References

1. Hugdahl K, Løberg EM, Specht K, et al. Auditory hallucinations in schizophrenia: the role of cognitive, brain structural and genetic disturbances in the left temporal lobe. *Frontiers in Human neuroscience*. 2008;28(1):6.
2. Regier DA, Narrow WE, Rae DS, et al. The de facto mental and addictive disorders service system. Epidemiologic Catchment Area prospective 1-year prevalence rates of disorders and services. *Archives of General Psychiatry*. 1993;50(2):85–94.
3. Rössler W, Salize HJ, Van Os J, et al. Size of burden of schizophrenia and psychotic disorders. *European Neuropsychopharmacology*. 2005;15(4):399–409.
4. Murray CJL, Lopez AD. The Global Burden of Disease. Harvard University Press, Cambridge, MA 1996. p. 21.
5. Dixon LB, Lehman AF, Levine J, et al. Conventional antipsychotic medications for schizophrenia. *Schizophrenia Bulletin*. 1995;21(4):567.
6. Buchanan RW, Kreyenbuhl J, Kelly DL, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophrenia Bulletin*. 2010;36(1):71.
7. Ereshefsky L, Mascarenas CA. Comparison of the effects of different routes of antipsychotic administration on pharmacokinetics and pharmacodynamics. *Journal of Clinical Psychiatry*. 2003; Suppl 64(16):18–23.
8. Kane JM, Kishimoto T, Correll CU, et al. Non-adherence to medication in patients with psychotic disorders: epidemiology, contributing factors and management strategies. *World Psychiatry*. 2013;12(3):216–226.
9. McEvoy JP, Byerly M, Hamer RM, et al. Effectiveness of paliperidone palmitate vs haloperidol decanoate for maintenance treatment of schizophrenia: a randomized clinical trial. *JAMA*. 2014;311(19):1978–1987.
10. Lieberman JA, Phillips M, Gu H, et al. Atypical and conventional antipsychotic drugs in treatment-naive first-episode schizophrenia: a 52-week randomized trial of clozapine vs chlorpromazine. *Neuropsychopharmacology*. 2003;28(5):995–1003.

11. Valenstein M, Blow FC, Copeland LA, et al. Poor antipsychotic adherence among patients with schizophrenia: medication and patient factors. *Schizophrenia Bulletin*. 2004;30(2):255.
12. Leucht S, Barnes TR, Kissling W, et al. Relapse prevention in schizophrenia with new-generation antipsychotics: A systematic review and exploratory metaanalysis of randomized, controlled trials. *American Journal of Psychiatry*. 2003;160:1209–1222.
13. Leucht S, Tardy M, Komossa K, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet*. 2012;379(9831):2063–2071.
14. Rosenheck RA, Krystal JH, Lew R, et al. Long-acting risperidone and oral antipsychotics in unstable schizophrenia. *New England Journal of Medicine*. 2011;364:842.
15. Chue P, Eerdekens M, Augustyns I, et al. Comparative efficacy and safety of long-acting risperidone and risperidone oral tablets. *European Neuropsychopharmacology*. 2005;15(1):111.
16. Deberdt R, Elens P, Berghmans W, et al. Intramuscular haloperidol decanoate for neuroleptic maintenance therapy. Efficacy, dosage schedule and plasma levels. An open multicenter study. *Acta Psychiatry Scandinavia*. 1980;62(4):356.
17. Kane JM, Sanchez R, Perry PP, et al. Aripiprazole intramuscular depot as maintenance treatment in patients with schizophrenia: a 52-week, multicenter, randomized, double-blind, placebo-controlled study. *Journal of Clinical Psychiatry*. 2012;73(5):617–624.
18. David A, Adams CE, Eisenbruch M, et al. Depot fluphenazine decanoate and enanthate for schizophrenia. *Cochrane Database Systematic Review*. 2005;(1):CD000307.
19. Marcus SC, Zummo J, Pettit AR, et al. Antipsychotic adherence and rehospitalization in schizophrenia patients receiving oral versus long-acting injectable antipsychotics following hospital discharge. *Journal of Managed Care & Specialty Pharmacy*. 2015;21(9):754–768.
20. Zuardi AW, Giampietro AC, Grassi ER. Double-blind comparison between two forms of haloperidol: An oral preparation and a new depot decanoate in the maintenance of schizophrenic inpatients. *Current Therapeutic Research*. 34:253–261.
21. Janssen-Ortho Inc. Janssen-Ortho Inc. Invega Sustenna. Product Monograph (2010) (revised 21 July 2010).
22. Chue P, Chue J. A critical appraisal of paliperidone long-acting injection in the treatment of schizoaffective disorder. *Therapeutic Clinical Risk Management*. 2016;27(12):109–116.
23. Kramer M, Litman R, Hough D, et al. Paliperidone palmitate, a potential long-acting treatment for patients with schizophrenia. Results of a randomized, double-blind, placebo-controlled efficacy and safety study. *International Journal of Neuropsychopharmacology*. 2010;13(5):635–647.
24. Samtani MN, Vermeulen A, Stuyckens K. Population pharmacokinetics of intramuscular paliperidone palmitate in patients with schizophrenia: A novel once-monthly, long-acting formulation of an atypical antipsychotic. *Clinical Pharmacokinetics*. 2009;48(9):585–600.
25. Pandina GJ, Lindenmayer JP, Lull J, et al. A randomized, placebo-controlled study to assess the efficacy and safety of 3 doses of paliperidone palmitate in adults with acutely exacerbated schizophrenia. *Journal of Clinical Psychopharmacology*. 2010;30(4):364.
26. Nasrallah HA, Gopal S, Gassmann-Mayer C, et al. A controlled, evidence-based trial of paliperidone palmitate, a long-acting injectable antipsychotic, in schizophrenia. *Neuropsychopharmacology*. 2010; 35(10):2072–2082.
27. Gopal S, Hough DW, Xu H, et al. Efficacy and safety of paliperidone palmitate in adult patients with acutely symptomatic schizophrenia: a randomized, double-blind, placebo-controlled, dose-response study. *International Clinical Psychopharmacology*. 2010;25(5):247–256.
28. Bossie CA, Sliwa JK, Ma YW, et al. Onset of efficacy and tolerability following the initiation dosing of long-acting paliperidone palmitate: post hoc analyses of a randomized, double-blind clinical trial. *BMC Psychiatry*. 2011;10(11):79.
29. Hough D, Gopal S, Vijapurkar U, et al. Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. *Schizophrenia Research*. 2010;116(2–3):107–117.
30. Sliwa JK, Bossie CA, Ma YW, et al. Effects of acute paliperidone palmitate treatment in subjects with schizophrenia recently treated with oral risperidone. *Schizophrenia Reearchs*. 2011;132(1):28–34.
31. Alphs L, Benson C, Cheshire-Kinney K, et al. Real-world outcomes of paliperidone palmitate compared to daily oral antipsychotic therapy in schizophrenia: a randomized, open-label, review board-blinded 15-month study. *Journal of Clinical Psychiatry*. 2015;76(5):554–561.
32. Doshi JA, Pettit AR, Stoddard JJ, et al. Concurrent Oral Antipsychotic Drug Use Among Schizophrenia Patients Initiated on Long-Acting Injectable Antipsychotics Post-Hospital Discharge. *Journal of Clinical Psychopharmacology*. 2015;35(4):442–446.
33. Gopal S, Berwaerts J, Nuamah I, et al. Number needed to treat and number needed to harm with paliperidone palmitate relative to long-acting haloperidol, bromperidol, and fluphenazine decanoate for treatment of patients with schizophrenia. *Neuropsychiatry Disease Treatment*. 2011(7):93–101.

34. Einarson TR, Zilbershtein R, Skoupá J, et al. Economic and clinical comparison of atypical depot antipsychotic drugs for treatment of chronic schizophrenia in the Czech Republic. *Journal of Medical Economy*. 2013;16(9):1089–1095.
35. Ravenstijn P, Remmerie B, Savitz A, et al. Pharmacokinetics, safety, and tolerability of paliperidone palmitate 3-month formulation in patients with schizophrenia: A phase-1, single-dose, randomized, open-label study. *Journal of Clinical Pharmacology*. 2016;56(3):330–339.
36. Gopal S, Vermeulen A, Nandy P, et al. Practical guidance for dosing and switching from paliperidone palmitate 1 monthly to 3 monthly formulation in schizophrenia. *Current Medical Resident Opinion*. 2015;31(11):2043–2054.
37. Berwaerts J, Liu Y, Gopal S, et al. Efficacy and safety of the 3-month formulation of paliperidone palmitate vs placebo for relapse prevention of schizophrenia: a randomized clinical trial. *JAMA Psychiatry*. 2015;72(8):830–839.
38. Savitz AJ, Xu H, Gopal S, et al. Efficacy and safety of paliperidone palmitate 3-month formulation for patients with schizophrenia: a randomized, multicenter, double-blind, noninferiority study. *International Journal of Neuropsychopharmacology*. 2016;19(7):pyw018.
39. Kishimoto T, Nitta M, Borenstein M, et al. Long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis of mirror-image studies. *Journal of Clinical Psychiatry*. 2013;74(10):957–965.

Key Words: aripiprazole, adverse effect, hypertension

Aripiprazole-induced Asymptomatic Hypertension: A Case Report

by Hilal Seven, Medine Giynaş Ayhan, Ayşe Kürkcü, Süleyman Özbek, İbrahim Eren

ABSTRACT *~ Aripiprazole is a second generation antipsychotic widely prescribed for the treatment of psychiatric diseases. It is generally known that antipsychotics have hypotensive effects. In this case report, however, we present the case of a medically healthy patient with schizophrenia who developed hypertension (HT) after the initiation of aripiprazole. The patient's blood pressure returned to normal after discontinuation of aripiprazole, suggesting that aripiprazole may have led to asymptomatic acute HT.* Psychopharmacology Bulletin. *2017;47(2):53–56.*

Introduction

Aripiprazole is a second-generation antipsychotic used safely in the treatment of schizophrenia, bipolar disorder and other psychiatric diseases because of milder metabolic side effects compared to other antipsychotics. Aripiprazole acts as a strong partial agonist of D2 and 5-HT1A receptors. Common side effects include headaches, sleeplessness, agitation and anxiety.[1] It has been reported that one of the most frequent cardiovascular side effect of second-generation antipsychotics is postural hypotension.[2] However, there is little information on the development of acute hypertension (HT) due to antipsychotics. Here, a case of acute HT induced by aripiprazole is reported and the possible mechanisms of HT are discussed.

Case

A 56 year-old woman with a 25-year history of schizophrenia was admitted to our clinic due to an acute exacerbation of her psychiatric disorder. Upon admission, loss of appetite, irritability, paranoid delusions and self-talking were present. Medical history and physical examination (including blood pressure) revealed no somatic disorder. No history of drug and alcohol abuse was reported. The patient had been treated for 2 years with olanzapine 10 mg/day and risperidone 37.5 mg/15 days and recovered partially. During the follow up period, olanzapine

Drs. Seven, Giynaş Ayhan, Kürkçü, Özbek, Eren, MD, Konya Training and Research Hospital, Department of Psychiatry, Konya, Turkey.

To whom correspondence should be addressed: Dr. Medine Giynaş Ayhan, MD, Konya Eğitim ve Araştirma Hastanesi, Psikiyatri Kliniği, 42250, Selçuklu-Konya, Turkey. E-mail: drmedineayhan@gmail.com

and risperidone were discontinued because of the adverse effects of sedation and weight gain. The patient underwent no treatment for 3 months until the current admission. The vital signs and blood tests were within normal limits in admission to the hospital. Aripiprazole 5 mg/day was then started, which was increased to 15 mg/day. About 9 days after the first intake of aripiprazole, blood pressure of 180/100 mmHg was measured indicating arterial HT. The patient had no symptoms like palpitation, headache or confusion. Physical examination (temperature, pulse), laboratory studies (complete blood count, liver and kidney function, serum electrolytes, lipids, coagulation) and electrocardiograms were within normal limits. She had no endocrine or reno-vascular disease that could explain the etiology of HT. Two days later aripiprazole was discontinued and the patient's HT resolved within 24 hours without treatment. At a subsequent follow up, the blood pressure was in the normal range.

Discussion

In the case report presented here, HT after the initiation of aripiprazole and recovery after aripiprazole discontinuation was observed. The case had no other medication or systemic disease that could explain the mechanism of HT. Based on these clinical features; it was thought that the patient developed asymptomatic HT due to aripiprazole.

It is well-known that second-generation antipsychotics may cause arrhythmia, prolonged QTc interval and orthostatic hypotension in patients who have no cardiovascular disease.[2] However, case reports suggest that HT may develop with the use of aripiprazole.[3–6] Borras et al. reported that a patient with schizophrenia who used aripiprazole 30 mg/day developed HT (220/110 mmHg) and tachycardia, and that the blood pressure returned to normal after discontinuation of aripiprazole.[3] Supporting this, another study reported that the blood pressure increased (200/110 mmHg) in a patient who was taking venlafaxine 150 mg/day and aripiprazole 5 mg/day and that the blood pressure decreased to normal 48 hours after stopping aripiprazole.[4] Additionally, Bat-Pitault and Derlome reported the development of HT in an adolescent patient taking aripiprazole.[5] Moreover, it was reported that a patient with depression using duloxetine 90 mg/day and aripiprazole 5 mg/day developed HT (220/110 mmHg) and headache. The blood pressure of this patient didn't respond to antihypertensive drugs and the HT resolved only after reducing the dose of aripiprazole to 2.5 mg/day.[6] In another case report, it was presented that the blood pressure increased after adding aripiprazole to the therapy; a decrease was seen after the discontinuation of aripiprazole.[7]

For the majority of the case reports mentioned above, it was thought that a history of HT or cardiovascular disease[4,7] and use of additional drugs[4,6] might have contributed to the increase in blood pressure. However, in the current case, as corroborated in the reports by Borras[3] and Pitault and Delorme's,[5] the patient had been using only aripiprazole and had no history of HT or cardiovascular disease. Moreover, other etiologic factors that may contribute to HT could not be found and it was observed that blood pressure resolved after stopping aripiprazole treatment.

It may be necessary to review the receptors that aripiprazole acts on to understand the mechanism of hypertension induced by aripiprazole. It is known that 5-HT 2A and a-1 adrenergic receptors play important roles in the development of hypertension.[8] Aripiprazole may cause an increase in blood pressure by binding with high affinity to the a-1A adrenergic receptors. It is also thought that aripiprazole causes HT by acting an as agonist for on 5-HT 2A receptors; however, this is controversial since some articles suggest that aripiprazole acts as an antagonist for 5-HT 2A receptors.[1] While one study suggested that use of aripiprazole resulted in higher blood pressure compared to placebo,[9] there are other studies that report that no relationship between the development of blood pressure abnormality and the use of aripiprazole.[10] Although individual differences may be important, these conflicting results need to be clarified with long term follow-up studies.

In this case report, we presented a case that developed asymptomatic HT with the use of aripiprazole, which resolved after the discontinuation aripiprazole. We think that this rare side effect seen in clinical practice should not be neglected and that blood pressure needs to be monitored closely regardless of whether the patient has a cardiovascular disease or not. ✤

Acknowledgements

The authors did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of Interest

None.

References

1. Di Sciascio G, Riva MA. Aripiprazole: from pharmacological profile to clinical use. *Neuropsychiatr Dis Treat*. 2015;11:2635–2647.
2. Pacher P, Kecskemeti V. Cardiovascular side effects of new antidepressants and antipsychotics: new drugs, old concerns? *Curr Pharm Des*. 2004;10:2463–2475.

3. Borras L, Constant EL, Eytan A, Huguelet P. Hypertension and aripiprazole. *Am J Psychiatry.* 2005;162:2392.
4. Pitchot W, Ansseau M. Aripiprazole, hypertension, and confusion. *J Neuropsychiatry Clin Neurosci.* 2010;22:123.
5. Bat-Pitault F, Delorme R. Aripiprazole and hypertension in adolescents. *J Child Adolesc Psychopharmacol.* 2009;19:601–602.
6. Hsiao YL, Chen SJ, Shen TW, Chang CH, Chen ST. Aripiprazole augmentation induced hypertension in major depressive disorder: a case report. *Prog Neuropsychopharmacol Biol Psychiatry.* 2011;35:305–306.
7. Yasui-Furukori N, Fujii A. Worsened hypertension control induced by aripiprazole. *Neuropsychiatr Dis Treat*. 2013;9:505–507.
8. Martin C, Brodde O-E, Insel PA. Peripheral adrenergic receptors in hypertension. *Hypertension.* 1990;16:107–120.
9. Keck PE Jr, Calabrese JR, McIntyre RS, McQuade RD, Carson WH, Eudicone JM, et al. Aripiprazole Study Group. Aripiprazole monotherapy for maintenance therapy in bipolar I disorder: a 100-week, double-blind study versus placebo. *J Clin Psychiatry.* 2007;68:1480–1491.
10. Findling RL, Robb A, Nyilas M, et al. A multiple-center, randomized, doubleblind, placebo-controlled study of oral aripiprazole for treatment of adolescents with schizophrenia. *Am J Psychiatry.* 2008;165:1432–1441.

Key Words: treatment-resistant schizophrenia, clozapine, aripiprazole, electroconvulsive therapy

Combined Antipsychotics and Electroconvulsive Therapy in an Acutely Psychotic Patient with Treatment-resistant Schizophrenia

by Ruth Rayikanti, Iga Lentowicz, Badari Birur, Li Li

ABSTRACT *~ Treatment of patients with Treatment-resistant Schizophrenia (TRS), who fail to respond to multiple antipsychotic trials, including clozapine (CLZ), is challenging. Several alternative strategies are reported in studies, one of which includes augmenting antipsychotics (AP) with Electroconvulsive therapy (ECT). We discuss a case of an acutely psychotic patient with TRS who responded effectively and sustained remission to this strategy which was ECT combined with two AP, CLZ and aripiprazole. Notable improvement in clinical and cognitive outcomes was seen with just five right unilateral ECT sessions, CLZ titrated up to 62.5 mg/d and aripiprazole 20 mg/d with no adverse effects. Nine days into the psychiatric hospitalization, patient had decreased total scores on the Positive and Negative Syndrome Scale by 44% and an improved score on the St. Louis University Mental Status Exam by increasing from 3 to 22. This case report suggests that a subgroup of patients with TRS could benefit from a trial of adjunct ECT combined with AP to achieve a rapid alleviation of positive and negative symptoms which allows patients to have greater functional stability.* Psychopharmacology Bulletin. *2017;47(2):57–62.*

Introduction

With a global prevalence of 1% and significant functional impairment, schizophrenia is a disabling disease.[1] Complicating this further is the heterogeneity among patient presentations, course of illness and treatment responses. Despite treatment with at least two adequate trials of antipsychotics (AP), 10%–30% of patients do not respond to treatment with AP and meet criteria for Treatment-resistant Schizophrenia (TRS).[2,3] Clozapine (CLZ) is recognized as the most effective AP medication for TRS, but a subgroup of 40%–70% fail to see an improvement with CLZ or require its suspension due to adverse effects such as neutropenia.[4] These patients often struggle with debilitating symptoms and face

Drs. Rayikanti, MD, Lentowicz, MD, Birur, MD, Li, MD, PhD, Department of Psychiatry and Behavioral Neurobiology, University of Alabama, Birmingham, AL, USA.

To whom correspondence should be addressed: Li Li, MD, PhD, Department of Psychiatry and Behavioral Neurobiology, University of Alabama, 1720 University Blvd., Birmingham, AL- 35294, USA. Phone: (205) 934-6269; Fax: (205) 975-4462; E-mail: liyli@uabmc.edu

a higher degree of functional and social disability.[5] Adjunct treatment strategies have been investigated, one of which is augmenting CLZ with Electroconvulsive therapy (ECT).[6] There is some preliminary evidence suggesting the safety and efficacy of CLZ augmentation with ECT (CLZ + ECT) in TRS.[7] Here we report a case of a 38 year-old female with TRS who responded effectively and sustained remission to this treatment strategy combining AP (i.e. CLZ + aripiprazole) with ECT.

Case Presentation

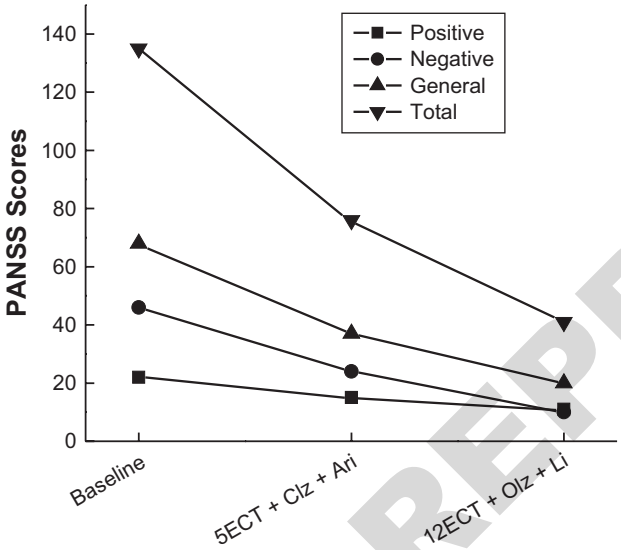
A 38 yrs. old Caucasian female presented to a local emergency room with a 2 week history of psychotic symptoms and cognitive impairment secondary to psychosis. Patient was diagnosed with TRS and has a history of Cannabis, Alcohol and Cocaine use disorder, but was in sustained remission for over 18 years under the care of assertive community treatment team (ACTT). One month prior to her presentation, she failed a second re-challenge with CLZ which was discontinued due to mild neutropenia with an Absolute Neutrophil Count (ANC) of 1400 μL (Normal range ANC 1500 μL in the general population). Patient was switched to aripiprazole (Ari) and titrated up to 20 mg/d and lorazepam 0.5 mg/d. However, this transition did not yield adequate control of symptoms. Following her admission, the Positive and Negative Syndrome scale (PANSS) was administered and she scored 135 out of 210, with prominent negative symptoms (Figure 1). Her acute cognitive impairment, as assessed by the St. Louis University Mental Status (SLUMS) exam was a total of 3. She had no significant past medical history or any active use of substances. After medical clearance, she agreed to a voluntary psychiatric hospitalization.

Patient's previous psychiatric admission was nearly 16 years ago, when she was first diagnosed with Schizophrenia at age 22. Since then, she had trials of quetiapine, risperidone, olanzapine and ziprasidone at adequate doses and duration before meeting criteria for TRS. For 9 years, she remained in partial remission on the most effective combination of AP, including CLZ 800 mg/d and ziprasidone 320 mg/d, along with bupropion XL 150 mg/d, clonazepam 1.5 mg/d and risperidone 3 mg/d as needed. Routine monthly blood draws were within normal limits for 8.5 years until bimonthly ANC monitoring was warranted. Six months later, a dramatic decrease in ANC was noted over two weeks (2100 μL to 1700 μL) warranting biweekly blood draws. She declined this level of monitoring and CLZ was discontinued at age 37.

Over that next year, multiple combinations of AP were attempted, and she had periods of non-compliance with medications. Later, she was adamant about being on a single AP; hence a second CLZ trial was

FIGURE 1

Positive and Negative Syndrome Scale (PANSS) was used to measure patient's response to combined treatments at the 3 time points: baseline, following 5 right unilateral ECTs and following 12 right unilateral ECTs



Abbreviations: Olz, olanzapine; Li, lithium; Ari, Aripiprazole.

started and titrated up to 800 mg/d, as monotherapy for 4 months, only to be suspended again due to mild neutropenia (ANC 1400 μL). It was this second CLZ discontinuation and replacement with Ari 20 mg/d that led to this current ER visit. Given the gravity of her presentation, she was re-challenged with her third CLZ trial started at 25 mg/d, and continued on Ari 20 mg/d.

Clinicians recognized the urgent necessity to alleviate symptoms, so they obtained consent from patient's mother to implement treatment with right unilateral ECT combined with two AP (CLZ + Ari). In just 9 days, patient had a significant clinical improvement with five right unilateral ECT sessions as adjunct to CLZ, titrated up slowly from 25 to 62.5 mg/d, while being maintained on Ari 20 mg/d with stable ANC counts at 2510 μL. Rating scales also correlated with this improvement: PANSS score decreased by 44% (total, and a more prominent reduction in negative than positive (47.8% vs. 32%) was noted. The SLUMS total score increased from 3 to 22, indicating the rapid response to this combined treatment. Noting her improvement, patient declined any further ECT, which was granted as she had medical decision capacity.

Slow titration of the third CLZ trial continued due to past history of neutropenia, though further improvement was slight and gradual

compared to the five ECT treatments. By the end of 34 days of hospitalization, patient's CLZ was titrated up to 200 mg/d, but required immediate discontinuation after ANC dropped to 1410 μL. CLZ was replaced with Olanzapine (Olz) 10 mg/d and within three days of this transition, ANC improved to 2100 μL. Given the prolonged hospitalization, her notable clinical and cognitive improvement, she requested to be discharged. With close ACTT weekly out-patient follow-up and patient being at her baseline mentation with non-bothersome hallucinations, she was deemed stable for discharge under her family's care on the following medications: Ari 20 mg/d, Olz 10 mg/d and mirtazapine 15 mg/d.

Four months later, patient discontinued Ari due to akathisia and lithium (1200 mg/d) was added to stabilize her mood. She has continued to decline any further re-challenges with CLZ to date due to her previous experiences. Eight months after the discharge from the hospital, she agreed to maintenance ECT and received 12 right unilateral treatments to target persistent positive symptoms, while being on the aforementioned doses of Lithium, Olz, and mirtazapine. Not only does she remain in partial remission to date, she has not required any further hospitalizations in over two years.

Discussion

Treatment of TRS is challenging. A staggering 40%–70% of TRS patients fails to respond to CLZ or is unable to tolerate it due to adverse effects leaving clinicians with the difficult task of finding alternate treatment strategies.[4,8] This subgroup faces insurmountable disabilities, has higher annual medical costs, and is often subject to frequent and prolonged hospitalizations compared to the non-TRS patients.[9,10] Multiple adjunct treatments to AP have been studied, including ECT. Current indications for the use of ECT in Schizophrenia are: prior response to ECT, ineffective pharmacotherapy and as second line for TRS.[11] Current data regarding this combined strategy stems mainly from case reports and open labeled trials, with limited information about implementing CLZ + ECT in patients who previously could not tolerate CLZ due to developing neutropenia, like the patient in this report.[12] Our case serves as an example for the safety and efficacy of this treatment strategy in TRS, especially with predominant negative symptoms.

In this reported case, clinicians required consideration of several factors in determining this patient's suitability for treatment with combined AP (CLZ + Ari) with ECT, including a past history of non-compliance with frequent blood draws, uncertainty over reinitiating a third CLZ trial in a patient who failed it twice due to neutropenia, her tolerance of this combined therapy and balancing her autonomy, beneficence and

non-maleficence given limited decision making capacity on admission. Based on a higher benefit versus risk ratio, the gravity of clinical presentation and lack of her capacity, informed consent was obtained from the patient's mother. Compared to the average ECT sessions for treatment of major depression, TRS patients likely need a higher number of treatments, with one systematic review finding the average to be 11.3 (range 4–20).[12,13] However, our patient achieved good results with just five right unilateral sessions, further supporting the growing evidence on the safety and effectiveness of this combined treatment strategy. Her rapid shift in symptoms correlated with improved total scores on SLUMS. Psychopathology as assessed by the PANSS also reflected her good response as seen by a decrease in all sub-scales, especially with the highest change in negative symptoms by 47.8% (Figure 1). This is significant as most previous studies found that severity rating scales saw higher reductions in positive symptoms with either little to no change or worsening of the negative symptoms in TRS with combination of CLZ + ECT.[14–16] There are likely multiple factors that may contribute to different observations between our case and others. This could include a much higher degree of illness severity prior to treatment, tools to assess severity changes (PANSS vs. other scales), combining specific AP like CLZ + Ari, frequency and type of ECT, patients' age and duration of psychotic episode.[12,17]

Conclusion

The combination of AP (CLZ + Ari) with adjunct ECT is safe and effective in improving prominent negative and cognitive symptoms in patients with TRS. This case report suggests that a subgroup of patients with TRS could benefit from a trial of adjunct ECT combined with AP to achieve a rapid alleviation of positive and negative symptoms which allows patients to have greater functional stability. Clinicians should consider this treatment option when managing patients with TRS. ✤

Acknowledgement

Authors would like to thank patient who provided informed consent for this case report.

References

1. Perala J, Suvisaari J, Saarni SI, et al. Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Archives of General Psychiatry*. 2007;64(1):19–28.
2. Schizophrenia AWGo. *Practice Guidelines for the Treatment of Patients with Schizophrenia, Second Edition*. American Psychiatric Association; 2004.

3. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Archives of General Psychiatry*. 1988;45(9):789–796.
4. Koen L vdBC, Niehaus DJH. Combining ECT and clozapine in the treatment of clozapine-refractory schizophrenia and schizoaffective disorder- a pilot study. *S Afr J Psychiatry*. 2008;14(4):131–135.
5. Meltzer HY. Defining treatment refractoriness in schizophrenia. *Schizophrenia Bulletin*. 1990;16(4): 563–565.
6. Masoudzadeh A, Khalilian AR. Comparative study of clozapine, electroshock and the combination of ECT with clozapine in treatment-resistant schizophrenic patients. *Pakistan Journal of Biological Sciences: PJBS*. 2007;10(23):4287–4290.
7. Kristensen D, Bauer J, Hageman I, Jorgensen MB. Electroconvulsive therapy for treating schizophrenia: a chart review of patients from two catchment areas. *European Archives of Psychiatry and Clinical Neuroscience*. 2011;261(6):425–432.
8. Petrides G, Malur C, Braga RJ, et al. Electroconvulsive therapy augmentation in clozapine-resistant schizophrenia: a prospective, randomized study. *The American Journal of Psychiatry*. 2015;172(1):52–58.
9. Hasan A, Falkai P, Wobrock T, et al. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, part 1: update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. *The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry*. 2012;13(5):318–378.
10. Kennedy JL, Altar CA, Taylor DL, Degtiar I, Hornberger JC. The social and economic burden of treatment-resistant schizophrenia: a systematic literature review. *International Clinical Psychopharmacology*. 2014;29(2):63–76.
11. Weiner RD CC, Fochtmann LJ, Greenberg RM, Isenberg KE, Kellner CH, Sackeim HA, Moench L. *The Practice of Electroconvlusive Therapy: Recommendations for Treatment, Training, and Privileging: a Task Force Report of the American Psychiatric Association, Indications for the use of Electroconvulsive Therapy*. Second ed. Washington D.C.: APA Inc.,; 2001.
12. Lally J, Tully J, Robertson D, Stubbs B, Gaughran F, MacCabe JH. Augmentation of clozapine with electroconvulsive therapy in treatment resistant schizophrenia: A systematic review and meta-analysis. *Schizophrenia Research*. 2016;171(1–3):215–224.
13. Kaplan H SB. *Kaplan & Sadock's Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry*. Tenth ed. Philadelphia: Wolter Kluwer/Lippincott Williams & Wilkins; 2007.
14. Pawelczyk T, Kolodziej-Kowalska E, Pawelczyk A, Rabe-Jablonska J. Augmentation of antipsychotics with electroconvulsive therapy in treatment-resistant schizophrenia patients with dominant negative symptoms: a pilot study of effectiveness. *Neuropsychobiology*. 2014;70(3):158–164.
15. Chanpattana W, Andrade C. ECT for treatment-resistant schizophrenia: a response from the far East to the UK. NICE report. *The Journal of ECT*. 2006;22(1):4–12.
16. Chanpattana W, Chakrabhand ML. Combined ECT and neuroleptic therapy in treatment-refractory schizophrenia: prediction of outcome. *Psychiatry Research*. 2001;105(1–2):107–115.
17. Furukawa TA, Levine SZ, Tanaka S, et al. Initial severity of schizophrenia and efficacy of antipsychotics: participant-level meta-analysis of 6 placebo-controlled studies. *JAMA Psychiatry*. 2015;72(1):14–21.

MEDWORKS MEDIA®
THE VOICE OF SCIENCE