表7 種々のガイドラインに見るうつ病軽症例に対する第一推奨治療（文献1, 4, 5, 14, 15, 16, 19, 22, 27, 28, 29, 30より一部改変）

精神科薬物療法研究会（JPAP）（日本） 2003	・SSRIかSNRI
埼玉薬物アルゴリズムプロジェクト（SMAP）（日本） 2006	・SSRI, SNRI
ベルリン 2003	・睡眠剝奪，次に抗うつ薬単剤
TMAP（テキサス） 2008	・エビデンスに基づいた心理療法が単独或いは薬物療法と併用で考慮されるべき ・さらに毎日の運動，適切な栄養摂取，ω-3脂肪酸，女性での葉酸も検討されるべき ・重症度で分けていないが薬物ならばSSRI，ブプロオン，ミルタザピン，SNRI
米国医学会・内科学会 2008	・非精神科医にとっては新規抗うつ薬
ハーバード 1998	・SSRIかブプロピオンでの十分な投与
カナダ 2004	・心理療法と薬物療法は同等
米国精神医学会（米国） 2006	・心理療法±薬物療法　・薬物療法は希望された場合 ・双方が必要な場合 a. 希望された場合 b. 単独の治療に対する部分反応歴 c. コンプライアンス不良
世界生物学的精神医学会（WFSBP） 2007	・教育，サポート，問題解決技法 ・心理療法が最初の治療モダリティとして考慮されるべき ・薬物療法はメインではない
オーストラリア・ニュージーランド 2004	・支持的な臨床ケアと心理教育が最も有効（薬物療法記載なし） ・問題解決技法や支持的カウンセリングによって補足される
NICE（英国） 2007	・薬物療法は初めの治療にリスクベネフィット比が低いため推奨しない ・患者が介入を希望しない場合，注意深く様子を観察し，待つ ・運動やうつ病についてのパンフレットを渡して指導 ・うつに焦点を当てた問題解決技法・簡単なCBT・カウンセリング ・長期のCBTやIPTは推奨されない

Making the right decision at the right time. Pharmacopsychiatry, 36 (suppl 3) : S222-S229, 2003

2) Akiskal, H.S., Benazzi, F.: Optimizing the detection of bipolar II disorder in outpatient private practice: toward a systematization of clinical diagnostic wisdom. J Clin Psychiatry, 66 (7) ; 914-921, 2005

3) American Psychiatric Association: Proposed Draft Revisions to DSM Disorders and Criteria (http://www.dsm5.org/ProposedRevisions/Pages/MoodDisorders.aspx)

4) Bauer, M., Bschor, T., Pfenning, A., et al.: World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders in primary care. The World Journal of Biological Psychiatry, 8 (2) ; 67-104, 2007

5) Canadian Network for Mood and Anxiety Treatments and the Canadian Psychiatric Association: Depression (MDD)-Diagnosis and Management. p. 1-15, 2004 (http://www.health.gov.bc.ca/gpac/pdf/depression_full_guideline.pdf)

6) Charles, C., Gafni, A., Whelan, T.: Decision-making in the physician-patient encounter: revisiting the shared treatment decision-making model. Soc Sci

Med, 49 (5) ; 651-661 1999

7) Cipriani, A., Furukawa, T.A., Salanti, G., et al.: Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet, 373 ; 746-758, 2009

8) Cooper, D., Moisan, J., Grégoire, J.P.: Adherence to atypical antipsychotic treatment among newly treated patients: a population-based study in schizophrenia. J Clin Psychiatry, 68 (6) ; 818-825, 2007

9) FDA Issues Public Health Advisory on Cautions for Use of Antidepressants in Adults and Children. FDA Talk Paper (http://www.fda.gov/bbs/topics/ANSWERS/2004/ANS01283.html)

10) Frank, E., Prien, R.F., Jarrett, R.B., et al.: Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. Arch Gen Psychiatry, 48 (9) ; 851-855, 1991

11) Ghaemi, S.N., Ko, J., Goodwin, F.K.: The Bipolar spectrum and the antidepressant view of the world. J Psychiatr Pract, 7 ; 287-297, 2001

12) Goldberg, J.F., Harrow, M., Whiteside, J.E.: Risk for bipolar illness in patients initially hospitalized for unipolar depression. Am J Psychiatry, 158 (8) ; 1265-1270, 2001

13) Harada, T., Sakamoto, K., Ishigooka, J.: Incidence and predictors of activation syndrome induced by antidepressants. Depress Anxiety, 25 ; 1014-1019, 2008

14) Harvard Medical School Department of Psychiatry, South Shore Residency Training Program: Algorithm for the Pharmacotherapy of Depression (http://mhc.com/Algorithms/ver4/depression/html/flowchar.htm)

15) 角田智哉，野村総一郎：薬物治療アルゴリズムの検証—TMAP と SMAP を通して．医学のあゆみ，219 ; 1063-1069, 2006

16) Karasu, T.B., Gelenberg, A., Merriam, A., et al.: Practice Guideline for the Treatment of Patients with Major Depressive Disorder Second Edition. American Psychiatric Association Practice Guideline for the Psychiatric Treatment. p. 763-840, 2006

17) Kikuchi, T., Uchida, H., Suzuki, T., et al.: Patients' attitudes toward side effects of antidepressants; An internet survey. European Archives of Psychiatry and Clinical Neuroscience (in press)

18) Melartin, T.K., Rytsala, H.J., Leskela, U.S., et al.: Continuity is the main challenge in treating major depressive disorder in psychiatric care. J Clin Psychiatry, 66 ; 220-227, 2005

19) National Institute for Health and Clinical Excellence: The treatment and management of depression in adults (http://www.nice.org.uk/nicemedia/live/12329/45888/45888.pdf)

20) Patrick, G., Combs, G., Gavagan, T.: Initiating antidepressant therapy? Try these 2 drugs first. J Fam Pract, 58 (7) ; 365-369, 2009

21) Qaseem, A., Snow, V., Denberg, T.D., et al.: Clinical Efficacy Assessment Subcommittee of American College of Physicians. Using second-generation antidepressants to treat depressive disorders: a clinical practice guideline from the American College of Physicians. Ann Intern Med, 149 : 725-733, 2008

22) Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression: Australian and New Zealand clinical practice guidelines for the treatment of depression. Australian and New Zealand Journal of Psychiatry, 38 ; 389-407, 2004

23) Rush, A.J., Fava, M., Wisniewski, S.R., et al.: Sequenced treatment alternatives to relieve depression (STAR*D) : rationale and design. Control Clin Trials, 25 (1) ; 119-142, 2004

24) Rush, A.J., Trivedi, M.H., Wisniewski, S.R., et al.: Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry, 163 (11) ; 1905-1917, 2006

25) Sachs, G.S., Nierenberg, A.A., Calabrese, J.R., et al.: Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med, 356 ; 1711-1722, 2007

26) Sawada, N., Uchida, H., Suzuki, T., et al.: Persistence and compliance to antidepressant treatment in patients with depression: a chart review. BMC Psychiatry, 16 ; 38, 2009

27) 塩江邦彦，平野雅巳，神庭重信：大うつ病性障害の治療アルゴリズム．気分障害の薬物治療アルゴリズム（精神科薬物療法研究会編集，本橋伸高責任編集）．じほう，

東京，p. 19-46, 2003

28) Sinclair, L.I., Christmas, D.M., Hood, S.D., et al.: Antidepressant-induced jitteriness/anxiety syndrome: systematic review. The British Journal of Psychiatry, 194; 483-490, 2009

29) TMAP (Texas Medication Algorithm Project) Manuals and algorithms: Major depressive disorder nonpsychotic algorithm (http://www.dshs.state.tx.us/mhprograms/pdf/TIMA_MDD_MDDAlgoOnly_080608.pdf)

30) 渡邊衡一郎，田　亮介，加藤元一郎：諸外国のうつ病治療ガイドライン・アルゴリズムにおける新規抗うつ薬の位置づけ―諸外国でもSSRI，SNRIは第一選択薬なのか．臨床精神薬理，11：1849-1859, 2008

31) 渡邊衡一郎，菊地俊暁：抗うつ薬服用者を対象としたウェブ調査2008の結果に見る患者の気持ち．臨床精神薬理，12；2295-2304, 2008

32) 渡邊衡一郎：うつ病の外来診療におけるヒント―お薬の上手な使い方について―．うつ病治療―現場の工夫より―．メディカルレビュー社，大阪，p. 208-232, 2010

The Changes in Pharmacotherapy for Depression

Koichiro WATANABE

Department of Neuropsychiatry, School of Medicine, Keio University

Since the introduction of the antidepressant fluvoxamine in 1999, pharmacotherapy has been recognised as the center of treatment for depression. However, recently, the relationship between a depressive state and using antidepressants is not as clear as it used to be. The treatment goal has changed from response to remission and recovery, and treatment adherence appears to be almost the same as that for schizophrenia. Regarding side effects, our research revealed that sleepiness and fatigue were ranked as the top two most burdensome side effects, and sometimes antidepressants cause anxiety and agitation, so clinicians are recommended to distinguish sedative antidepressants from non-sedatives. After the year 2000, the debate regarding underdiagnosing bipolar disorder emerged. Finally, looking at major treatment guidelines for depression around the world, for moderate depression, pharmacotherapy remains the first-line treatment, but, for mild depression, the guidelines recommend guided self-help, walking, and problem-solving techniques, etc., which can be understood as tools to promote resilience. So, treating depression now seems more complicated and difficult compared to the 1990's.

<Author's abstract>

臨床精神薬理 13：2227-2235, 2010

うつ病の治療ガイドライン・アルゴリズムに見る現在のうつ病治療における薬物療法の立ち位置，そしてわが国における実現可能性は？

渡邊 衡一郎* 冨田 真幸*

抄録：諸外国のうつ病の治療ガイドラインにおいて，軽症例では薬物療法は推奨されず，心理療法や運動，栄養面への配慮，パンフレットを渡す，支持的ケア，問題解決技法といった簡単なケアを勧めている。今後これら非薬物療法の実際の効果およびわが国の環境に導入可能かどうかなど，様々な観点から検討する必要があるだろう。なお中等症例においては，ほとんどのガイドラインで薬物療法が推奨されているが，心理療法を同等に扱っているものも多い。ただ薬物療法と言っても，新規抗うつ薬が決して推奨されているわけでない。薬物を選択する際には患者の嗜好，事前の反応，症状，身体合併症，費用，利益と忍容性とのバランス等において考慮すべきとしている。しかしこうした治療ガイドラインの策定には，薬物療法の専門家よりも，むしろ心理士や健康経済学者のほうが多く加わっていたりする。エビデンスの質の高さよりも医療経済的な要素やこの分野における国や自治体の方針が反映されているようである。ガイドラインを読む際にはこうした状況をよく理解する必要があるだろう。 臨床精神薬理 13：2227-2235, 2010

Key words：*antidepressant, resilience, treatment guideline, depression*

Ⅰ．はじめに

筆者らは2008年10月本誌で，「諸外国のうつ病治療ガイドライン・アルゴリズムにおける新規抗うつ薬の位置づけ」という題の論文を執筆した[21]。当時諸外国のガイドラインに見る幅広い治療選択肢に驚きながら，そこで示された薬物療法以外の治療法のわが国における実現可能性についてこれまで模索して来た。対費用効果や患者の治療に対する本音など，我々がこれまで比較的軽視してきた要素を考慮に入れ，心理療法や簡単かつ身近なアプローチの必要性など多くのものをガイドラインから学べた。そこから2年経った今，改訂されたガイドラインも一部あることから，若干その論文の記載と重複するが，ここで改めて諸外国のガイドライン・アルゴリズムに見る，2010年現在のうつ病治療における薬物療法の立ち位置がどうなっているか検討したい。

Ⅱ．我が国の治療アルゴリズムの紹介

日本精神科薬物療法研究会（JPAP）による我が国のうつ病治療のアルゴリズムでは，軽症から中等症例においては新規抗うつ薬を推すが，重症例になると従来型抗うつ薬の使用を推奨している[16]。これはSSRI（1999年にfluvoxamineが上

The positioning of pharmacotherapy in various treatment guidelines of depression.

*慶應義塾大学医学部精神神経科学教室
〔〒160-8582 東京都新宿区信濃町35〕
Koichiro Watanabe, Masayuki Tomita : Department of Neuropsychiatry, School of Medicine, Keio University. 35, Shinanomachi, Shinjuku-ku, Tokyo, 160-8582, Japan.

市）とSNRIが導入された後の2001年～2002年にJPAPが7パターンのうつ病症例を呈示して診断や治療に関するアンケートを実施し，その結果に国内外のエビデンスやレビューなどを加えて誕生したものである。アンケートの協力者によって症例の一部で軽症と中等症の判断が分かれたこともあり，このアルゴリズムでは一括して「軽症ならびに中等症」とされている。なお欧米では軽症が独立し，むしろ中等症～重症が一括りとなっていることが多い。

Ⅲ．諸外国のガイドライン・アルゴリズムを概観する

現在多くのガイドライン・アルゴリズムが発表されているが，今回再びうつ病の軽症・中等症例における治療・対応，あるいは薬物を選択する際の注意点をまとめた。

1．軽症例（表1）

わが国では，先述のJPAP[16]，そして埼玉のアルゴリズム（SMAP）[7]においても軽症例は中等症例と一緒に扱われ，新規抗うつ薬SSRI，SNRIが推奨されている。他にもドイツのベルリン[1]，米国のハーバードのアルゴリズム[6]，国際的なプロジェクトであるIPAP[19]においてもJPAP，SMAPと同様，新規抗うつ薬の使用が推奨されている。2008年の米国医学会・内科学会のものでは，それまで三環系抗うつ薬，ハーブであるセントジョンズワート（オトギリ草）が推されていたが，今回新規抗うつ薬のみが推奨された[13]。

米国精神医学会（APA）[8]，カナダ[4]では心理療法と薬物療法を同等に扱い推奨している。2008年の米国のTMAPでは新規抗うつ薬を推奨しつつも，薬物治療のアルゴリズムでありながら心理療法も共に推奨し，さらには運動，栄養面への配慮，ω-3脂肪酸，葉酸など手軽に取り組めるものを同様に勧めている[18]。しかし英国NICE[12]，オーストラリア・ニュージーランド[14]，そして生物学的治療を専門とする研究者が参加する生物学的精神医学会世界連合（WFSBP）のガイドライン[2]では，まず第一に注意深い観察や運動，うつ病に関するパンフレットを渡す，支持的ケア，問題解決技法等を推奨し，その次に簡単な認知行動療法（CBT）やカウンセリングが挙げられている。プラセボと差がなくリスク・ベネフィット比が小さいからということで，薬物療法は最初の治療選択肢として考えられていないようである。さらにNICEでは長期のCBTや対人関係療法（IPT）といった構造化された心理療法までも推奨されていない[12]。我が国でもCBTが保険適応となったが，少なくとも軽症例に関するこうした指摘を理解しておくことが求められる。

今後これらガイドラインで挙げられている非薬物療法のエビデンスを調べ，それぞれのメリット・デメリットを把握すること，さらにはわが国の環境にこれらのアプローチを導入することが可能かどうか，マンパワー，制度，コスト等の点から検討する必要があるだろう。

2．中等症例（表2）

中等症例においては，一転してほとんどのガイドラインで薬物療法が推奨されている。しかしどのカテゴリーの薬物と具体的に謳っていないものが多く，さらに米国（APA）[8]，英国（NICE）[12]，カナダ[4]，オーストラリア[14]，そしてWFSBP[2]では薬物療法と心理療法を同等に扱っており，心理療法の中ではCBTやIPTが推奨されている。

米国の大規模臨床試験STAR*D試験（中等症例が多くエントリー）において第一選択のSSRIであるcitalopramによる寛解例が36.8%で，第二選択のあらゆる新規抗うつ薬による増強あるいは置換，さらには認知療法の導入などを試みても30.6%程度しか加えて寛解しなかったという状況を鑑みると[15]，ただ機械的に治療法を変えるのでなく，患者の病状によって治療法を工夫することも検討課題になると思われる。

3．薬物を選択する際に考慮すべき点（表3）

抗うつ薬の選択について，わが国と同様に新規抗うつ薬の使用を推奨しているのは英国（NICE）[12]，TMAP[18]，米国内科学会・医学会[13]のみである。三環系抗うつ薬と効果は同等だが，副作用での中断が起きにくいからというのが理由と

表1　軽症例に対する第一推奨治療

精神科薬物療法研究会(JPAP) 2003[16]	SSRI，SNRI
SMAP(埼玉) 2006[7]	SSRI，SNRI
ベルリン 2003[1]	睡眠剥奪，次に抗うつ薬単剤
国際精神薬理アルゴリズムプロジェクト(IPAP) 1995[19]	特に重症度で分けていないが，SSRIがメインで，nefazodone，bupropion(NDRI)，venlafaxine(SNRI)，moclobemide(RIMA)，mirtazapine(NaSSA)が代替の選択肢
ハーバード 1998[6]	SSRIかbupropionでの十分な投与
米国医学会・内科学会 2008[13]	特に重症度で分けていないが非精神科医にとっては新規抗うつ薬
カナダ 2004[4]	心理療法と薬物療法は同等
APA(米国) 2006[9]	・心理療法±薬物療法 ・薬物療法は希望された場合 ・双方が必要な場合　a. 希望された場合 b. 単独の治療に対する部分 c. コンプライアンス不良
豪国・ニュージーランド 2004[14]	・支持的な臨床ケアと心理教育が最も有効(薬物療法記載なし) ・問題解決技法や支持的カウンセリングによって補足される
WFSBP 2007[2]	・教育，サポート，問題解決技法 ・心理療法が最初の治療モダリティとして考慮されるべき ・薬物療法はメインではない
TMAP(テキサス) 2008[18]	・エビデンスに基づいた心理療法が単独あるいは薬物療法と併用で考慮されるべき ・毎日の運動，適切な栄養摂取，ω-3脂肪酸，女性での葉酸も検討されるべき ・重症度で分けていないが薬物ならばSSRI，bupropion，mirtazapine，SNRI
NICE(英国) 2007[12]	・薬物療法は初めの治療にリスクベネフィット比が低いため推奨しない ・患者が介入を希望しない場合，注意深く様子観察し，待つ ・運動やうつ病についてのパンフレットを渡して指導 ・うつに焦点を当てた問題解決技法 ・簡単なCBT・カウンセリング ・長期のCBTやIPTは推奨しない

なる。

他のガイドラインではカテゴリー別に選択するのではなく，薬物を選択する際に患者の嗜好，事前の反応，症状，身体合併症，費用，利益と安全性と忍容性とのバランス等において考慮すべきとしている。薬物における患者の嗜好の中には，効果面を重視するか，あるいは患者の好まざる副作用の少なさが関与している。ただ気にしない，または好まざる副作用は個々の患者において大きく異なる。各薬物のプロフィールを熟知し説明することが求められる。

このように軽症および中等症うつ病に関して，諸外国では必ずしも薬物療法を第一選択としていない。また薬物療法とはいっても必ずしも新規うつ薬が第一推奨とされていない。新規抗うつ薬は過量服薬による致死性が少ないことを含め使いやすいというメリットはあるが，催奇形性やアクティベーション・シンドローム，中断症候群，消

表2　中等症例に対する第一推奨治療

精神科薬物療法研究会(JPAP) 2003[16]	SSRI, SNRI
SMAP(埼玉) 2006[7]	SSRI, SNRI
国際精神薬理アルゴリズム プロジェクト(IPAP) 1995[19]	特に重症度で分けていないが，SSRIがメインで，nefazodone, bupropion(NDRI)，venlafaxine(SNRI)，moclobemide(RIMA)，mirtazapine(NaSSA)が代替の選択肢
ハーバード 1998[6]	SSRIかbupropionでの十分な投与
STAR*D 2006[15]	SSRI(citalopram)
米国医学会・内科学会 2008[13]	特に重症度で分けていないが非精神科医にとっては新規抗うつ薬
TMAP(テキサス) 2008[18]	SSRI, bupropion, mirtazapine, SNRI(venlafaxine)
ベルリン 2003[1]	睡眠剥奪，次に抗うつ薬単剤
WFSBP 2007[2]	・抗うつ薬±心理療法 ・心理社会的介入
APA(米国) 2006[3]	・薬物±有効な心理療法(ECTが予定されていなければ) ・心理療法＋薬物あるいはECT(心理社会的問題が重要だったり，患者が望めば) ・双方が必要な場合 a. 顕著な心理社会的問題　b. 対人関係問題 c. パーソナリティ障害　d. コンプライアンス不良
NICE(英国) 2007[12]	・心理学的介入より前に抗うつ薬が投与されるべき ・社会的サポート ・長期の構造化された心理学的介入(CBT)
カナダ 2004[4]	・薬物療法 ・心理療法(CBT, IPT, 問題解決技法) ・薬物＋心理療法は単独以上の効果はない
豪国・ニュージーランド 2004[14]	・ほとんどすべての抗うつ薬とCBT, IPTが同等に有効 ・治療選択や継続において同意が可能となるような良好な治療関係を築くことによって，最大の利益が得られる

化器症状，性機能障害など，むしろ新規抗うつ薬の方で多く見られると考えられる副作用もある。さらに当然のことながら従来薬に比してそれなりにコストがかかるためか，諸外国のガイドライン上では所詮選択肢の1つにしか過ぎないということになる。

わが国ではSSRI・SNRI，そしてNaSSAの導入により，現在までに多くの抗うつ薬を使用することが可能となった。既存のガイドラインやアルゴリズムを参考にしながら，少なくとも我々精神科医は各薬剤のプロフィールを熟知し，目の前の患者と効果や副作用，費用等に関して議論し，治療法を選択すること，さらにはそうした情報を他科の医師に伝えていくことが求められるといえよう。

Ⅳ. ガイドライン策定の背景にあるもの

本来治療ガイドラインはそれまでに発表された

表3　薬物選択で考慮すべき要素

	患者の嗜好	事前の反応	症状	身体合併症	身体治療併用薬	薬物への家族の反応	薬物相互作用	費用	副作用	臨床試験のデータ	新規抗うつ薬推奨	自殺の危険性	その他
JPAP		○	○	○	○	○		○	○		○	○	年齢，入院か外来か，心理・社会適応レベル，支援システムの強度
WFSBP	○	○		○	○	○	○	○	○				事前のアドヒアランス
APA	○	○		○	○	○		○	○	○			精神科的併存症状
NICE	○	○	○						○		○	○	
TMAP	○	○		○	○	○					○		1日1回投与，他の新規抗うつ薬も
カナダ		○	○	○	○		○	○	○				短期の寛解率
豪・NZ									○				利益と危険性のバランス
ACP	○							○	○		○		TCAも

文献21)を一部改変

エビデンスを吟味し，その質の高さ（メタ解析や大規模試験などでの証明が優先される）を基に策定されることが多い。ここでガイドラインはいかにして作られるのか，2009年に発表された英国NICEガイドラインを例にとって検証してみたい[12]。このNICEガイドラインの策定委員は，総勢35名。驚くことにうつ病を経験した患者が2名，また介護する者も1名参加しているのが画期的である。ガイドラインには種々の治療に対する患者の視点までも記載されている。医師は一般開業医（GP）が2名，心理の専門医も1名入っているが，薬物療法を専門とする者は入っていない。薬剤師1名，心理療法の専門家は4名（その内1名はCBTの専門家），看護師が2名，さらに健康経済学者が3名も入っている。あとは疫学専門家や評論家などである。この一般臨床からすると些か偏った人数バランスにおいても明らかなように，心理的アプローチとコストの問題により焦点が当てられて検討された結果であると分かる。このため薬物療法と心理療法，問題解決技法などについて推奨しながらも，健康経済学者の影響か，薬物療法だけでなく長期のCBTやIPTまでも推奨しないという記載や，ほとんど無料で可能な簡単なケアを推奨しているのだと思われる。何よりも英国はOECD加盟国の内，医療費が最低水準なのである。このように低コストかつ多職種で策定チームが構成されたため，エビデンスのレベルよりも，むしろ各団体の気負いが強く出た結果なのではないかとまで勘ぐってしまう。ガイドラインを読む際はこうした状況をよく理解して読み込む必要があるだろう。

V．薬物療法は推奨されないのか？

諸外国のガイドラインを概観すると，軽症うつ病に対しては抗うつ薬を初めとする侵襲性の高いしっかりとした治療というよりは，適切な方向に少し背中を押してあげるようなアプローチが推奨されているといえる。このような例については認知の歪みも軽度なため，本人の持つ自己回復力（レジリアンス）やプラセボ効果が発揮されやすい状態と考えられる。

プラセボと比較した抗うつ薬の効果を再検証する興味深い論文が発表された。Fournier ら[9]はFDAに報告された大うつ病および小うつ病の外来患者対象の最低6週間の無作為化プラセボ対照比較試験を抽出し，その結果6研究（718名の患者）が選定された。HDRSが23点より低いとエフェクトサイズで薬物とプラセボと差が認められるCohenのdが0.20より低かった。試験前の重症度が増すと薬物とプラセボとの差はつき，ようやく25点で初めてNICEでプラセボと意義ある差とされる0.20以上の差をつけた。このことから，軽症か中等症の患者にはプラセボと同等であり，重症例でないと差がつかないとしたのである。

軽症うつ病に対して抗うつ薬の効果はプラセボ効果を上回らない可能性については理解できるが，だからといって軽症うつ病に抗うつ薬が効かないということにはならないだろう。軽症うつ病に対してもしっかりと評価し，フォローしていく必要はあり，その結果ケースによっては抗うつ薬の適応となる可能性がある。軽症うつ病ではプラセボ効果が比較的発揮されやすい状態にあり，治療者としてはプラセボ効果や最近指摘されているレジリアンスを妨げないようなアプローチを考えることが大切なようだ。なお，プラセボといえども，入院治療による反応者では脳内に変化をもたらすことがPETで指摘されている[10]。

最近こうした考えにマスコミが注目し，ガイドライン策定の裏にある各国のお国柄や医療政策に関する種々の意図を無視し，その表に出て来る記載のみにこだわった偏った報道をしている印象がある。それはマスコミの鳴らす薬物療法至上主義に対する警鐘と同義と考える。マスコミはなぜにここまで抗うつ薬を悪玉として見なしたいのだろうか。現に多くの人が抗うつ薬によって自殺を回避し，休職をしていた人の多くが復職を可能としている。わが国の研究でも年代別にSSRIの処方数の推移と自殺との関係を表したものがあるが，自殺率は各年代ごとに検証すれば年々減少している[11]。これまで非定型抗精神病薬のメタボリックな副作用の問題は緊急安全性情報にまで至ったのに対し，うつに関しては自殺他に関する添付文書の改訂はあるが，そこまでには至っていない。

Ⅵ．薬物療法の適応を改めて考える

しかし，なぜか社会問題になっているこの状況を冷静に考えると，反省すべき点として，我々精神科医自身があまりに無頓着に製薬会社のキャンペーンに乗ってしまい，うつ状態でさえあればとりあえず抗うつ薬を投与して患者の様子を見ようとしてきたことが挙げられる。ある薬がだめなら他の薬に変えるか次々と追加していく。あるいは本来適応でない人にも安易に使用し，その結果，投与早期や増量後に見られやすいとされるアクティベーション・シンドロームを増やしてしまったと思われる[22]。最近抗うつ薬2剤併用の効果が単剤のそれよりも優れるという報告も出されたが[3]，それをさらに上回る3剤など理論の伴わない多剤併用療法が新薬が登場するたびに増えたかもしれない。最近では非定型抗精神病薬による増強療法もよく目にする。向精神薬だけでも4～5種服用している処方で‘治療抵抗性’として外来で相談されることも多い。

我々は抗うつ薬を処方すればとりあえずどうにかなるという期待でここまで来たが，双極性の問題，アクティベーション・シンドロームなど投与後のその先を鋭く予測することが求められる。

DSM-Ⅲ[17]はうつを広めたという。しかし今ここで我々治療者は己にとっての抗うつ薬処方の適応を一時的に狭くして，この先何が起こるか用心しながら薬剤を投与すべきかも知れない。

英米のプライマリーケアの現場におけるうつ病患者の嗜好についての研究をまとめたレビューでは，初診患者の3～4割しか薬物療法を希望しておらず，残りは心理療法を希望していた（表4）。薬物療法は依存性や副作用が怖いから希望せず，逆に心理療法は病気の原因を治してくれる治療法という期待が大きかったという[20]。

CBTがわが国でも保険適応となり，その恩恵に浴する患者が増えるだろう。しかしながらやみくもに行うのではなく，きちんと患者の気持ちを踏まえて行うことが必要である。薬物療法もレジリアンスを十分刺激すると考えられているが，患者の期待に反した治療を施せば，それは到底患者

表4　プライマリーケア医にかかるうつ病患者の治療の好み

著者	国	年齢(歳)	参加者数	心理療法やカウンセリングを好んだ者(%)	抗うつ薬を好んだ者(%)
Bedi, 2000 Chilvers, 2001	UK	18－70	220	64　C	36
Dwight-Johnson, 2000, 2001	USA	18－90	1187	55　C	27
King, 2000 Ward, 2000	UK	≧18	457	43　C 26　PT	20
Simpson, 2000	UK	18－70	180	66　C	28
Unützer, 2002	USA	≧60	1801	51　PT	38

C：カウンセリング，PT：心理療法　　文献20)を一部改変

のレジリアンスを刺激するはずもない。こうした患者の期待に沿うような治療法や医師-患者関係の確固たる構築こそ，レジリアンスすなわち自己回復力を刺激するのではないだろうか。

Ⅶ．わが国における実現可能性

さて，本稿に示したような治療法がそのままわが国の臨床にすぐ応用できるのであろうか。

ここで今後のわが国のお手本となるであろう英国の現状について小堀ら[9]が詳細に紹介しているので，本稿で一部紹介する。

抑うつか不安の問題に苦しんでいる人の半数は，16セッションのCBTを受ければ，1人あたり15万円以下の予算で回復することが見積もられている。多くの人は薬物療法よりCBTのような心理療法を好んでいるにもかかわらず，英国でもこれまで現実にCBTを受けられる利用者は限られていた。

なお，英国で臨床心理士とは，博士号を持ち，主にCBTを使う人たちのことを指す。抑うつや不安の問題が生じ，家庭医（GP）を訪問してから専門機関へと紹介され，心理療法が始まるまでに多くの時間がかかった（最長で18ヵ月）。待機期間が長いのは，臨床心理士の人手不足が主な原因だったという。

またセッション外の時間が長いため（アセスメント，セッションの準備，記録の振り返り，スーパービジョン，書類作成など），1人の臨床心理士が行えるセッション数が限られていることも，このアクセスの難しさに影響していた。

英国イングランドにおいて，心理療法へのアクセスを改善させるための政策（Improving Access to Psychological Therapies：IAPT）が始まり，2008年からの3年間で合計363億円が費やされたという。セラピスト1人が1年で持つクライアントは80人で，80万人を回復させるために，最終的に1万人のセラピストを増やすことが計画され，ソーシャル・ワーカーや看護師，医師などがセラピストとして養成されるらしい。

日本では臨床心理士による心理療法が保険点数化されておらず，専門的な心理療法を実践できる医師の数も少ない。医師1名に対する患者数も多く，患者1人当たりの診療時間を十分に確保することができていないのが現状である。こうした限界の中で結果として短時間で解決できて患者もそれなりに軽快し，かつ満足する治療として現状では薬物療法を中心に捉えざるを得ない。医師数を増やしていく，あるいは心理療法を可能とする質の高い専門家を育成すると同時に，心理療法や運動療法などの非薬物療法をより手軽に行えるようになるには，政策レベルでの動きがどうしても必要である。それを実現するために我々現場の精神科医ができることは一体何であるのか，漫然と日々の臨床に追われるだけでなく，それを常に念頭に置くべきであろう。

Ⅷ. おわりに

各種うつ病のガイドラインを概観すると，薬物療法は中等症例以上では推奨されているが，軽症例では，次善の策に位置している感がある。プライマリーケアを受診するうつ病患者の6割以上が心理療法を希望しているという事実，また運動療法や簡単なサポートが有効とのエビデンスがあることを我々は十分知っておく必要がある。ただCBTも，イギリスでさえつい先日まで前述のような状況であった。今後CBTが広く受け入れられる状況が整備されるまでは，忙しい臨床の中で薬物療法をとりあえずというよりはレジリアンスを刺激することを意識し，薬物療法はその中の1つの策として考えながら施行することが望ましいだろう。そうすることで薬物療法という最大の効果を発揮するツールが最大限活かされ，1人でも多くの患者が寛解，回復そして社会に戻っていけるのではないかと思う。

文　献

1) Adli, M., Rush, A. J., Möller, H. -J. et al. : Algorithms for optimizing the treatment of depression : making the right decision at the right time. Pharmacopsychiatry, 36 (suppl. 3) : S222-S229, 2003.
2) Bauer, M., Bschor, T., Pfennig, A. et al. : World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders in Primary Care. World J. Biol. Psychiatry, 8(2) : 67-104, 2007.
3) Blier, P., Ward, H. E., Tremblay, P. et al. : Combination of antidepressant medications from treatment initiation for major depressive disorder : a double-blind randomized study. Am. J. Psychiatry, 167(3) : 281-288, 2010.
4) Canadian Network for Mood and Anxiety Treatments and the Canadian Psychiatric Association : Depression (MDD)-Diagnosis and Management : 1-15, 2004. http://www.health.gov.bc.ca/gpac/pdf/depression_full_guideline.pdf
5) Fournier, J. C., DeRubeis, R. J., Hollon, S. D. et al. : Antidepressant drug effects and depression severity : a patient-level meta-analysis. JAMA, 303(1) : 47-53, 2010.
6) Harvard ハーバード大学アルゴリズム　http://mhc.com/Algorithms/ver4/depression/html/flowchar.htm
7) 角田智哉，野村総一郎：薬物治療アルゴリズムの検証—TMAPとSMAPを通して．医学のあゆみ，219 (13) : 1063-1069, 2006.
8) Karasu, T. B., Gelenberg, A., Merriam, A. et al. : Practice Guideline for the Treatment of Patients with Major Depressive Disorder Second Edition. pp. 763-840, American Psychiatric Association, Arlington, 2006.
9) 小堀 修，清水栄司，伊豫雅臣：イギリスの認知行動療法セラピストを7年で10,000人養成する計画．千葉医学雑誌，85 : 93-95, 2009.
10) Mayberg, H. S., Silva, J. A., Brannan, S. K. et al. : The functional neuroanatomy of the placebo effect. Am. J. Psychiatry, 159(5) : 728-737, 2002.
11) Nakagawa, A., Grunebaum, M. F., Ellis, S. P. et al. : Association of suicide and antidepressant prescription rates in Japan, 1999-2003. J. Clin. Psychiatry, 68 : 908-916, 2007.
12) National Institute for Health and Clinical Excellence : Depression : The treatment and management of depression in adults. http://www.nice.org.uk/nicemedia/live/12329/45888/45888.pdf
13) Qaseem, A., Snow, V., Denberg, T. D. et al. ; Clinical Efficacy Assessment Subcommittee of American College of physicians : Using second-generation antidepressants to treat depressive disorders : a clinical practice guideline from the American College of Physicians. Ann. Intern. Med., 149(10) : 725-733, 2008.
14) Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for Depression : Australian and New Zealand clinical practice guidelines for the treatment of depression. Aust. N. Z. J. Psychiatry, 38 : 389-407, 2004.
15) Rush, A. J., Trivedi, M. H., Wisniewski, S. R. et al. : Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps : a STAR*D report. Am. J. Psychiatry, 163(11) : 1905-1917, 2006.
16) 塩江邦彦，平野雅巳，神庭重信：大うつ病性障害の治療アルゴリズム．気分障害の薬物治療アルゴリズム(精神科薬物療法研究会 編集，本橋伸高 責任編集)，pp. 19-46, じほう，東京，2003.

17) 高橋三郎，花田耕一，藤縄 昭 訳：DSM-Ⅲ精神障害の分類と診断の手引．医学書院，東京，1982.
18) Texas-Department of State Health Services : Algorithm for the Treatment of Major Depressive Disorder. http://www.dshs.state.tx.us/mhprograms/pdf/TIMA_MDD_MDDAlgoOnly_080608.pdf
19) Trivedi, M. H., DeBattista, C., Fawcett, J. et al. : Developing treatment algorithms for unipolar depression in cyberspace : International Psychopharmacology Algorithm Project(IPAP). Psychopharmacol. Bull., 34 (3) : 355-359, 1998.
20) van Schaik, D. J., Klijin, A. F., Van Hout, H. P. et al. : Patients' preferences in the treatment of depressive disorder in primary care. Gen. Hosp. Psychiatry, 26 (3) : 184-189, 2004.
21) 渡邊衡一郎，田 亮介，加藤元一郎：諸外国のうつ病治療ガイドライン・アルゴリズムにおける新規抗うつ薬の位置づけ―諸外国でもSSRI, SNRIは第一選択薬なのか．臨床精神薬理，11 : 1849-1859, 2008.
22) 渡邊衡一郎：新規抗うつ薬と攻撃性との関係性．日本医師会雑誌，138 : 2289-2291, 2010.

Magnitude of Rater Differences in Assessment Scales for Schizophrenia

Takefumi Suzuki, MD, PhD,†‡ Hiroyoshi Takeuchi, MD,* Shinichiro Nakajima, MD,* Kensuke Nomura, MD,* Hiroyuki Uchida, MD, PhD,*† Gohei Yagi, MD, PhD,* Koichiro Watanabe, MD, PhD,* and Haruo Kashima, MD, PhD**

Abstract: The magnitude of rater differences, instead of interrater reliability, in the assessment scales of schizophrenia has rarely been investigated and was therefore addressed in this study.

Thirty-six patients with schizophrenia were independently assessed by 4 expert physicians, using clinical rating scales including the Positive and Negative Syndrome Scale (PANSS). The scores obtained by the physician in charge (PIC), who had a long close contact with the patients, served as the referent answer for the purpose of this study. The scores rated by the other 3 non-PIC psychiatrists, who had a first formal examination with them, were evaluated for percentage deviance from the referent answer.

The results showed that the PIC raters endorsed the numerically highest score in 20 (56%) of the 36 patients, whereas they rated the lowest in only 2 (6%) in the PANSS total score. The non-PIC assessors on the average underrated the PANSS total score by 10%, and such a tendency of underestimating the severity was noted across other clinical scales. Furthermore, the PANSS total score by one of the non-PIC physicians was deviant from the referent answer by at least 20% in 15 (42%) of 36 instances. Importantly, this magnitude of deviance was noted in the context of an intraclass correlation coefficient of 0.92.

This unique investigation disclosed clinically pertinent differences among raters, even under an excellent interrater reliability. The magnitude of differences described herein seems to be an underestimation, and the baseline scores by the independent new raters might need to be corrected for those by the PICs.

Key Words: assessment, interrater reliability, PANSS, rater differences, schizophrenia, validity

(*J Clin Psychopharmacol* 2010;30: 607–611)

Establishing a good interrater reliability of the assessments scales is of utmost importance in integrity for schizophrenia studies because the assessments are likely to be performed by multiple assessors, especially for large multisite interventions. Moreover, the baseline assessments would have a critical effect on the subsequent ratings in an effort to trace changes. Therefore, it is crucial to get as accurate as possible baseline scores, which would not infrequently be obtained at the very first systematic encounter with the subjects.

However, although it is typical to demonstrate interrater reliability by means of intraclass correlation coefficient (ICC) and so forth, the magnitude of rater differences (ie, interrater disagreement) in the assessment scales for schizophrenia contrarily has never been specifically targeted in the literature to the best of the authors' knowledge. This study addressed this critical issue using a unique strategy.

METHODS

This is a reanalysis of previously reported patients.[1] In short, to develop user-friendly assessment scales in schizophrenia, the newly developed Functional Assessment for Comprehensive Treatment of Schizophrenia (FACT-Sz) and Targeted Inventory on Problems in Schizophrenia (TIP-Sz) were tested against the Positive and Negative Syndrome Scale (PANSS),[2] the Clinical Global Impression (CGI)—severity subscale,[3] and the Global Assessment of Functioning (GAF), to assess their reliability and validity. The TIP-Sz assesses 10 common problems in patients with schizophrenia and FACT-Sz global functioning.[1]

In that study, 36 patients with schizophrenia were assessed by 4 expert psychiatrists, all with substantial clinical experience in psychopharmacology.[4–9] T.S., H.T., and S.N. had been serving as the physician in charge (PIC) with a long-term alliance with the patients (each responsible for 12 patients). Apart from the examinations made by the PICs for their own patients, all encounters were the brand-new systematic interview with the patients, a situation that closely resembles the baseline assessment in clinical studies. Collateral information included a medical chart, usually with a brief summary of the patient.

All assessments were made independently on a one-to-one encounter basis, to create 4 × 36 assessment data for each rating scale (raters × patients). These assessments took place in a random order taking into account availability of the patients and the assessors. All patients were examined on the same day, and care was taken to rate outpatients around early afternoon. Adequate time was allowed for the first-time examinations (up to 1 hour).

For the purpose of this study, the assessment scores by the PICs on their own patients served as the referent answer, and they were compared with the scores by the rest of the 3 raters (ie, non-PICs) for percentage deviance in scores. As for the PANSS, it was rated with a score of 1 to 7, and the nondeductible value was also taken into account for data presentation (eg, the most deviant score by one of the 3 non-PIC raters minus the referent answer) divided by [referent answer minus 30] in the case of total score).[10]

For instance, assume a total score in the PANSS by the PIC for some patient is 90 and those rated by the non-PICs are 93, 84, and 78. Each value represents a +3% (corrected, +5%), −7% (corrected, −10%), and −13% (corrected, −20%) deviance from the referent answer. Next, assume a total score by the PIC for another patient is 100 and those rated by the non-PICs are 94, 91, and 110. Each value represents a −6% (corrected, −9%), −9% (corrected, −13%), and +10% (corrected, +14%) deviance. In the first instance, the most deviant value is −20%, and

From the *Department of Neuropsychiatry, School of Medicine, Keio University, Tokyo, Japan; †Centre for Addiction and Mental Health; and ‡Department of Psychiatry, University of Toronto, Toronto, Canada.
Received February 26, 2010; accepted after revision July 7, 2010.
Reprints: Takefumi Suzuki, MD, PhD, Department of Neuropsychiatry, School of Medicine, Keio University, 35, Shinanomachi, Shinjuku-ku, Tokyo, 160-8582, Japan (e-mail: takefumi@oak.dti.ne.jp).
This work did not receive any financial support.

ISSN: 0271-0749
DOI: 10.1097/JCP.0b013e3181f0bae1

TABLE 1. Magnitude of Deviance From Referent Answer by 3 Non-PIC Raters Averaged

	PANSS—Total	PANSS—Positive	PANSS—Negative	PANSS—General	CGI—Severity	GAF	TIP-Sz	FACT-Sz
Mean (total)	−6% (corrected, −10%)	−4% (corrected, −6%)	−6% (corrected, −8%)	−7% (corrected, −10%)	−3%	+5%	+2%	+2%
Mean (inpatients)	−5% (corrected, −6%)	−3% (corrected, −3%)	−3% (corrected, −4%)	−5% (corrected, −7%)	−1%	+7%	+2%	+3%
Mean (outpatients)	−8% (corrected, −13%)	−6% (corrected, −8%)	−8% (corrected, −13%)	−9% (corrected, −14%)	−5%	+4%	+3%	+1%

Raw scores by PICs were as follows (mean ± SD): 100 ± 21 (PANSS—total), 24 ± 7 (PANSS—positive), 26 ± 7 (PANSS—negative), 51 ± 11 (PANS—general), 4.6 ± 1.0 (CGI—severity), 43 ± 14 (GAF), 60 ± 14 (TIP-Sz), and 53 ± 18 (FACT-Sz).

a mean deviance is calculated as −8% among the non-PIC raters (corrected). They are +14% and −3%, respectively, in the second example. Such data were obtained across all 36 patients.

Table 1 presented the mean deviance across the 3 non-PIC raters (−5% in the previously mentioned examples). Table 2 described the corrected maximum/minimum deviance by one of the 3 non-PICs (+14%/−20% in the previously mentioned examples). Table 3 showed a frequency of clinically relevant deviance in which one of the 3 non-PICs endorsed a score that was deviant from the referent answer by 10% and 20% or more (both of the previously mentioned cases are included in 10% or more deviance, and only the first is included in 20% or more deviance). These analyses were applied to the PANSS subscales and other clinical scales.

This post hoc analysis was not a predetermined one when the original study had been performed, obviating a systematic bias if any at the time of the assessments. The original study was granted by the institutional review board of each participating site, and written informed consent had been obtained from all patients. This reanalysis was approved by each site and waived for additional informed consent from the subjects, as the data have already been made completely anonymous. Statistical analyses were performed with SPSS (version 17.0, SPPS Inc, Chicago, Ill).

RESULTS

The study sample was characterized with serious symptoms or functional impairments (ie, mean ± SD GAF score of 44 ± 14). Half of the patients were inpatients. Patients exhibited moderate to marked severity in illness (ie, CGI—severity score of 4.5 ± 1.2), with the mean PANSS total score across all 4 raters being 95 ± 22 (inpatients, 108 ± 19; outpatients, 82 ± 15). These values corresponded nicely to those in a large number of subjects by Rabinowitz et al.[11] Across the 4 raters, the mean PANSS total score for all 36 patients ranged from 92 to 100, suggesting a good concordance. In fact, the overall interrater and intrarater correlations among the scales have been shown to be good to excellent in the original study (ie, ICCs of 0.82–0.97, Spearman's ρs of 0.83–0.91).[1]

However, the PICs endorsed the numerically highest score in 20 (56%) of the 36 patients, whereas they rated the lowest in only 2 (6%). Moreover, the PANSS total scores by the PICs were numerically higher than the calculated mean scores by 3 non-PICs in 29 patients (81%). This corresponded to a 10% underestimation by the non-PICs in the PANSS total score (nondeductible value corrected). Raters unfamiliar with the patients (ie, other 3 non-PIC evaluators) tended to underestimate the severity in all of the assessment scales that were investigated in this study (note that the status of a patient is more severe if a score is higher in the PANSS and CGI—severity and if a score is lower in the GAF, TIP-Sz, and FACT-Sz; Table 1).

Furthermore, the magnitude of deviance in each assessment scale from the referent answer was not negligible, and one of the 3 non-PIC raters gave a score that was deviant from −46% to +29% with respect to the PANSS total score (Table 2). Across 36 patients, one of the 3 non-PICs gave a score that is 2 or more points deviant from the referent answer in 28% for the PANSS all items, 26% for positive subscale items, 27% for negative subscale items, and 30% for general psychopathological subscale items.

Table 3 shows frequencies of clinically relevant deviance from the referent answer by one of the non-PIC raters. At least a 10% deviance from the referent answer was found to represent a majority (29/36 patients, which means that all 4 raters agreed in the PANSS total score within <10% variance in only 7 patients). In addition, one of the non-PIC evaluators gave a PANSS score

TABLE 2. Magnitude of Deviance From Referent Answer by 1 of 3 Non-PIC Raters

	PANSS—Total	PANSS—Positive	PANSS—Negative	PANSS—General	CGI—Severity	GAF	TIP-Sz	FACT-Sz
Maximum (total)	+19% (corrected, +29%)	+45% (corrected, +100%)	+23% (corrected, +33%)	+35% (corrected, +63%)	+33%	+38%	+31%	+40%
Maximum (inpatients)	+19% (corrected, +28%)	+45% (corrected, +69%)	+23% (corrected, +33%)	+35% (corrected, +56%)	+25%	+38%	+31%	+40%
Maximum (outpatients)	+13% (corrected, +29%)	+21% (corrected, +100%)	+18% (corrected, +27%)	+21% (corrected, +63%)	+33%	+33%	+23%	+16%
Minimum (total)	−28% (corrected, −46%)	−42% (corrected: −100%)	−29% (corrected, −60%)	−32% (corrected, −55%)	−50%	−17%	−20%	−22%
Minimum (inpatients)	−28% (corrected, −43%)	−42% (corrected: −59%)	−29% (corrected, −36%)	−26% (corrected, −41%)	−20%	−17%	−20%	−22%
Minimum (outpatients)	−26% (corrected, −46%)	−31% (corrected: −100%)	−29% (corrected, −60%)	−32% (corrected, −55%)	−50%	−15%	−13%	−13%

TABLE 3. Frequency of Relevant Deviance From Referent Answer by 1 of 3 Non-PIC Raters

	PANSS—Total	PANSS—Positive	PANSS—Negative	PANSS—General	CGI—Severity	GAF	TIP-Sz	FACT-Sz
10% or more deviance (total)	67% (corrected, 81%)	72% (corrected, 89%)	86% (corrected, 92%)	94% (corrected, 100%)	75%	69%	61%	64%
10% or more deviance (inpatients)	61% (corrected, 72%)	72% (corrected, 89%)	83% (corrected, 83%)	100% (corrected, 100%)	67%	78%	78%	83%
10% or more deviance (outpatients)	72% (corrected, 89%)	72% (corrected, 89%)	89% (corrected, 100%)	89% (corrected, 100%)	83%	61%	44%	44%
20% or more deviance (total)	8% (corrected, 42%)	33% (corrected, 56%)	33% (corrected, 69%)	36% (corrected, 78%)	61%	22%	14%	22%
20% or more deviance (inpatients)	6% (corrected, 22%)	33% (corrected, 44%)	33% (corrected, 61%)	28% (corrected, 67%)	39%	33%	22%	44%
20% or more deviance (outpatients)	11% (corrected, 61%)	33% (corrected, 67%)	33% (corrected, 78%)	44% (corrected, 89%)	83%	11%	6%	0%

that was more than 20% higher than the referent answer in 3 patients and at least 20% lower in as many as 13 occasions. Only for 1 patient, one of the non-PIC raters gave a total PANSS rating that is higher than 20% from the correct answer and another non-PIC lower than 20%. As such, a 20% or more deviance was noted in 15 (42%) of 36 patients.

Of high pertinence here is that such a magnitude of variability was observed in the context of an ICC of 0.92 in the PANSS total score overall ($P = 0.000$),[1] which would be generally considered excellent. It was found that deviance in the PANSS score was generally more pronounced among outpatients (Tables 1 and 3).

DISCUSSION

The PANSS has been and will continue to be used as the primary outcome in many studies for schizophrenia.[12] The larger the clinical trial, the higher the chance that clinical assessments are performed by multiple raters. Randomized trials frequently adopt independent raters, and the baseline assessment score is likely to be obtained at the very first systematic encounter with the patients, to provide a basis for longitudinal evaluations. These facts notwithstanding, the magnitude of rater differences have not been adequately explored thus far.

To briefly highlight the issue of rater differences in the assessment scales, a PubMed search using keywords of *PANSS*, *rater*, and *reliability* was conducted, only yielding 27 hits (May 2010), and none seemed to have specifically focused on the magnitude of rater disagreement (instead of agreement). The results were similar if the word *reliability* was replaced with *validity* (24 hits).

Although measuring the correct answer in the rating scale is not without challenges, this study regarded the score by the PICs as the referent answer, and the scores from the 3 non-PIC raters were assessed for deviance. The results of this unique investigation disclosed that the expert raters who met the patients for the first time and thus are unfamiliar with them tended to underestimate in the assessment scores, compared with the PICs who are in much closer contact with the patients being examined. The magnitude of deviance was not clinically negligible, and an overall 10% underestimation in the PANSS total score was associated with the first-time encounters. Of high pertinence is that such a degree of difference was noted under an excellent reliability (ICC, 0.92) among the 4 expert raters.

Furthermore, one of the expert non-PIC psychiatrists was deviant from the referent answer by at least 20% in 42% of the patients examined. This represents a significant message that the baseline score can already be different to such a magnitude. Here, it is important to remember that a 20% change in the PANSS total score represents a meaningful effect, especially for challenging population (ie, a 20% decrease frequently defines response in treatment-resistant schizophrenia).

That the deviance in the PANSS score was generally more pronounced among outpatients is a highly expected finding because they had lower scores whereby a same absolute deviance results in a relatively higher percentage difference compared with higher scores (note that a 10-point lower score means a 20% deviance if the referent answer is 80, but it equals to a 10% deviance if the referent answer is 130). This point is nonetheless crucial, in that many patients in clinical studies are likely to show a score range of the outpatients in this study (typically 60's to 80's in the PANSS), rather than that of inpatients.

A lack of longitudinal assessment is a limitation. Alternatively, addressed here was a cross-sectional interrater disagreement (ie, rater effect) and not a longitudinal intrarater unreliability (ie, rater drift). In addition, sample size was limited. The authors do not rule out a possibility that 4 assessments might have made the patients tired to respond suboptimally. However, the patients were assessed in the same day, were generally cooperative, and indicated a favorable impression for rather lengthy interviews. Furthermore, we believe that the 4 raters are well experienced enough to professionally elucidate symptoms further upon suspicion and have made the encounters as comfortable as possible. As such, the data presented herein may well be a very conservative estimation.

The findings might not argue against a possibility of overrating by the PICs, but the authors believe that they would be more naturally interpreted as underscoring by the non-PIC assessors, given a plausible possibility that a one-shot interview misses things that somebody who knows a patient better can appreciate.

Nevertheless, a lack of adjustment for order effect of the interviews (eg, patients might express themselves better in the first assessment than the fourth assessment), interval between the interviews (ie, status of patients might change even within the day), and a lack of subjective psychodynamic perspective (ie, response of the patients may vary depending on psychological comfort at the time of the encounter with the assessors) all need to be acknowledged as confounders. Because ICC provides a composite of intrarater and interrater variabilities, the former effect might have been diluted given that one of the non-PICs gave a score that is 2 or more points deviant from the referent answer in 28% for the PANSS all items.

The strategy described herein is not necessarily confined to the assessment scales for schizophrenia but may be applicable to other objectively measured rating scales in psychiatry. The findings taken together underscore a need for further studies to investigate the magnitude of rater differences and more importantly to search for factors on rater disagreement in the assessment scales of schizophrenia. Finally, future studies might better compare the baseline scores by the independent raters with those by the physicians who are familiar with the subject very well, for potential corrections in data as appropriate.

ACKNOWLEDGMENT

The authors thank Dr Akira Tanabe, who passed away in May 2009, for his unstinted support.

AUTHOR DISCLOSURE INFORMATION

All authors do not have any conflict of interests in relation to this article. Dr Suzuki's fellowship has been supported by the Government of Canada Post-Doctoral Research Fellowships, Japanese Society of Clinical Neuropsychopharmacology, Kanae Foundation, and Mochida Memorial Foundation.

REFERENCES

1. Suzuki T, Uchida H, Nomura K, et al. Novel rating scales for schizophrenia—Targeted Inventory on Problems in Schizophrenia (TIP-Sz) and Functional Assessment for Comprehensive Treatment of Schizophrenia (FACT-Sz). *Schizophr Res*. 2008;106: 328–336.
2. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. *Schizophr Bull*. 1987;13:261–276.
3. Guy W. *ECDEU Assessment Manual for Psychopharmacology—Revised (DHEW Publ No ADM 76-338)*. Rockville, MD: US Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, NIMH Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976:218–222.

4. Nakajima S, Uchida H, Suzuki T, et al. An open-label trial of discontinuing benzodiazepines in patients with chronic schizophrenia. *J Clin Psychopharmacol.* 2007;27:401–403.
5. Suzuki T, Uchida H, Watanabe K, et al. Effectiveness of antipsychotic polypharmacy for patients with treatment refractory schizophrenia: an open-label trial of olanzapine plus risperidone for those who failed to respond to a sequential treatment with olanzapine, quetiapine and risperidone. *Hum Psychopharmacol.* 2008;23:455–463.
6. Takeuchi H, Suzuki T, Uchida H, et al. A randomized, open-label comparison of 2 switching strategies to aripiprazole treatment in patients with schizophrenia: add-on, wait, and tapering of previous antipsychotics versus add-on and simultaneous tapering. *J Clin Psychopharmacol.* 2008;28:540–543.
7. Nakajima S, Ishida T, Akaishi R, et al. Impacts of switching antidepressants after successful electroconvulsive therapy on the maintenance of clinical remission in patients with treatment-resistant depression: a chart review. *J ECT.* 2009;25:178–181.
8. Suzuki T, Uchida H, Takeuchi H, et al. Augmentation of atypical antipsychotics with valproic acid. An open-label study for most difficult patients with schizophrenia. *Hum Psychopharmacol.* 2009;24:628–638.
9. Uchida H, Suzuki T, Mamo DC, et al. Survey of benzodiazepine and antidepressant use in outpatients with mood disorders in Japan. *Psychiatry Clin Neurosci.* 2009;63:244–246.
10. Leucht S, Davis JM, Engel RR, et al. Definitions of response and remission in schizophrenia: recommendations for their use and their presentation. *Acta Psychiatr Scand Suppl.* 2009;119(s438):7–14.
11. Rabinowitz J, Mehnert A, Eerdekens M. To what extent do the PANSS and CGI-S overlap? *J Clin Psychopharmacol.* 2006; 26:303–307.
12. Suzuki T, Uchida H, Watanabe K, et al. Treatment target in schizophrenia: a critical review and a clinical suggestion. *Psychopharmacol Bull.* 2008;41:80–101.

Clinical and Demographic Characteristics Associated With Postural Instability in Patients With Schizophrenia

Akihiro Koreki, MD, Kenichi Tsunoda, MD, PhD,† Takefumi Suzuki, MD, PhD,*‡§ Jinichi Hirano, MD,|| Koichiro Watanabe, MD, PhD,*|| Haruo Kashima, MD, PhD,* and Hiroyuki Uchida, MD, PhD*†‡*

Abstract: As people with schizophrenia grow older, prevention of falls in this older population has become a public health priority. It is therefore critically important to identify risk factors to effectively prevent falls. For this purpose, the degree of postural sway can serve as a convenient index of risk assessment. The objective of this study was to find clinical and demographic characteristics associated with postural instability. Inpatients and outpatients with schizophrenia or related psychosis were recruited at 2 hospitals in Japan. The clinical stabilometric platform, which measured a range of the trunk motion, and extrapyramidal side effects were evaluated between 9 and 11 A.M. Four hundred two subjects were enrolled (age: mean, 55.5 [SD, 14.4] years). A univariate general linear model showed that the use of antipsychotic drugs with a chlorpromazine equivalent of 10 or greater, being overweight, and inpatient treatment setting were associated with a greater degree of the range of postural sway. Another general linear model, including a subgroup of 300 subjects who did not present any extrapyramidal side effects, not only consolidated these findings, but also revealed a great degree of postural sway in older subjects. In addition, quetiapine was found to be associated with a greater range of postural sway among atypical antipsychotics. Schizophrenia patients generally showed a greater degree of postural instability, compared with the reference data of healthy people. These findings highlight truncal instability as a risk factor of falls in patients with schizophrenia, especially when they are overweight, old, and/or receiving antipsychotics with a chlorpromazine equivalent of 10 or greater, including quetiapine.

Key Words: aging, antipsychotic, postural sway, quetiapine, schizophrenia, adverse effect

(*J Clin Psychopharmacol* 2011;31: 16–21)

Aging is associated with a higher risk of falls[1] that often lead to serious consequences such as fractures, which in turn reduces the activities of daily living and the quality of life.[2] This risk would be expected to be especially higher in people who receive psychotropic drugs, including antipsychotic drugs, as the risk of falls has been reported to be escalated by the use of those drugs.[3,4] Furthermore, older people are more frequently and seriously susceptible to adverse effects of these medications because of their age-related increased sensitivity to psychotropic drugs.[5–8] Among old population groups, people with schizophrenia should be paid special attention to because almost all of them have received psychotropic treatment until their late life.[9] As people with schizophrenia grow older, prevention of falls in this older population has become a public health priority. To effectively prevent falls, it is critically important to identify risk factors of falls.

Identifying risk factors of falls, including specific class of medications and body mass index (BMI), presents some difficulties. Although this requires a long-term follow-up, those clinical factors are subject to change during the follow-up period in reality. Indeed, previous studies demonstrated an association of the use of psychotropic drugs with falls, but failed to specify which drug or how much dose was related with a greater incidence of falls.[3,4] Furthermore, BMI is also changeable in the long run, making it an unstable marker. On the other hand, postural sway is a convenient measure to assess the stability of body posture and has been reported to be associated with the risk of falls.[1,10] Postural sway can be assessed in a cross-sectional fashion, which enables us to relate the degree of sway with currently prescribed medications as well as BMI. To our knowledge, there has been only 1 study investigating postural sway in patients with schizophrenia.[11] They demonstrated that patients with schizophrenia have subtle, yet quantifiable, disturbances in the control of posture, but failed to demonstrate differential drug effect. However, this negative finding may be due to a type II error derived from a small sample size of 36.

In this study, we therefore evaluated the postural sway and identified factors that were associated with instability in body posture in a large number of schizophrenia patients. Moreover, the data from schizophrenia patients were also compared with the normative data with a focus on age.

METHODS

In this cross-sectional study, subjects were eligible if they were 16 years or older, were diagnosed with schizophrenia or related psychotic disorder (F20–F29 according to the *International Classification of Mental and Behavioural Disorders, 10th Edition*),[12] and had been receiving a steady medication regimen for at least 1 week. This study was conducted at the Minamihannou Hospital, Saitama, Japan, and Ohizumi Hospital, Tokyo, Japan, between October and November 2009. Subjects in this study had received both computed tomography and electroencephalography upon their first visit to one of the participating sites as a part of the routine clinical screening examination and an annual follow-up electroencephalography thereafter. Subjects who showed any significantly abnormal finding in these assessments were excluded. The study was approved by the institutional review board at each participating site, and subjects provided written informed consent after receiving detailed information about the protocol.

From the *Department of Neuropsychiatry, Keio University School of Medicine, Tokyo; †Department of Psychiatry, Minamihanno Hospital, Saitama, Japan; ‡Geriatric Mental Health Program, Centre for Addiction and Mental Health; §Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada; and ||Department of Psychiatry, Ohizumi Hospital, Tokyo, Japan.

Received February 6, 2010; accepted after revision November 9, 2010.

Reprints: Hiroyuki Uchida, MD, PhD, Department of Neuropsychiatry, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan (e-mail: mcn41320@biglobe.ne.jp).

This study has not been presented.

ISSN: 0271-0749
DOI: 10.1097/JCP.0b013e318205e192

The following were clinically assessed between 9 and 11 A.M.: postural sway and extrapyramidal side effects (EPSs). The stability of the standing body was assessed, using the clinical stabilometric platform (GS-7; ANIMA, Tokyo, Japan), which measures the range of the trunk motion by evaluating the resistance applied to the platform for 30 seconds, with eyes closed and with feet together. The position of the center of pressure as the subject stands on the platform was calculated from forces and moments. The outcome measure is a measure of center-of-pressure sway area surrounded by an outer line, which is automatically calculated by this device and shown as values in centimeters squared. Smaller range indicates a better stability. Extrapyramidal side effects were assessed, using the Simpson-Angus Scale,[13] the Barnes Rating Scale for Drug-Induced Akathisia,[14] and the Abnormal Involuntary Movement Scale.[15] Subjects who did not show any positive score on any item in the Simpson-Angus Scale, Barnes Rating Scale for Drug-Induced Akathisia, or Abnormal Involuntary Movement Scale were regarded as those without EPSs.

In addition, the collected information included age, sex, body weight, height, and psychotropic medications prescribed. Daily doses of antipsychotics, including depot antipsychotics, were converted to chlorpromazine equivalents (CPZEs) (Table 1).[16,17] For further analysis, antipsychotic drugs were divided based on their (ie, <10 or ≥10 mg/d). For subjects who were receiving more than 1 antipsychotic drug, a sum of CPZE for all prescribed antipsychotic medications was calculated, and a main antipsychotic drug was defined as one that accounted for a majority of the daily CPZE dose. Subjects who received CPZE less than 300 mg/d and CPZE 600 mg/d or greater were considered to belong to low- and high-dose groups, respectively, whereas others were sorted to a standard dose group, in accordance with the Schizophrenia Patient Outcomes Research Team Treatment Recommendations.[18]

Statistical analyses were carried out, using SPSS version 17.0 (SPSS Inc, Chicago, Ill). First, a univariate general linear model was used to examine the effects of age group (ie, <50 [young] or ≥50 [old]); sex; BMI (ie, <18.5 kg/m^2 [underweight], 18.5–25.0 kg/m^2 [standard], >25.0 kg/m^2 [overweight]); class of main antipsychotic drugs (ie, CPZE ≥10 or <10) or individual atypical antipsychotics (ie, risperidone, olanzapine, quetiapine, or aripiprazole); dose of antipsychotic drugs (ie, low-, standard-, or high-dose group); the use of benzodiazepines, mood stabilizers, antiepileptic drugs, lithium, anticholinergics, and antihypertensives; and treatment settings (ie, inpatient or outpatient) on the range of trunk motion. This model was generated with main effects and all 2-way interaction terms. After this preliminary analysis, the variables that were not found to have any statistically significant effect on the range (ie, the use of mood stabilizers, antiepileptic drugs, lithium, anticholinergics, and antihypertensives) were excluded from the following model to enhance the statistical power. In the main analysis, another general linear model was generated with the rest of the main effects and all significant 2-way interaction terms. When appropriate, we also examined group differences with pairwise comparisons, using Tukey-Kramer HSD (honestly significant difference). $P < 0.05$ was considered statistically significant, and all tests were 2-tailed.

TABLE 1. Relative Potency of Prescribed Antipsychotic Drugs

Antipsychotics With a CPZE of <10		Antipsychotics With a CPZE of ≥10	
Risperidone	1 (n = 144)	Perphenazine	10 (n = 1)
Timiperone	1.3 (n = 5)	Propericiazine	40 (n = 5)
Haloperidol	2 (n = 72)	Clocapramine	40 (n = 1)
Bromperidol	2 (n = 12)	Quetiapine	66 (n = 21)
Fluphenazine	2 (n = 4)	Zotepine	66 (n = 6)
Olanzapine	2.5 (n = 60)	Levomepromazine	100 (n = 7)
Pimozide	4 (n = 1)	Chlorpromazine	100 (n = 6)
Aripiprazole	4 (n = 21)	Sulpiride	200 (n = 3)
Blonanserin	4 (n = 11)		
Nemonapride	4.5 (n = 1)		
Perospirone	8 (n = 10)		
Chlorpromazine 100 mg/d			
Haloperidol decanoate 30 mg/4 wk (n = 5)			
Fluphenazine decanoate 7.5 mg/2 wk (n = 6)			

TABLE 2. Demographic and Clinical Characteristics of 402 Subjects

Characteristics	Values
Age, mean (SD) (range), y	55.5 (14.3) (16–88)
<50 y, n (%)	148 (36.8)
≥50 y, n (%)	254 (63.2)
Male, n (%)	249 (61.9)
Main antipsychotic drug	
Antipsychotics with a CPZE of <10, n (%)	352 (87.6)
Antipsychotic with a CPZE of ≥10, n (%)	50 (12.4)
Antipsychotic dose, n (%)	
<300 mg/d CPZE	94 (23.4)
300–599 mg/d CPZE	104 (25.9)
≥600 mg/d CPZE	204 (50.7)
Benzodiazepine use rate, n (%)	309 (76.9)
BMI, n (%)	
<18.5 kg/m^2	38 (9.4)
18.5–24.9 kg/m^2	237 (59.0)
≥25.0 kg/m^2	127 (31.6)
Treatment Setting, n (%)	
Inpatient	351 (87.3)
Outpatient	51 (12.7)

RESULTS

A total of 402 subjects were included. Demographic and clinical characteristics are summarized in Table 2. Psychiatric diagnoses of subjects were as follows: schizophrenia (n = 388), schizoaffective disorder (n = 5), delusional disorder (n = 3), psychotic disorder NOS (n = 3), and acute and transient psychotic disorder (n = 3). The 5 most frequently prescribed antipsychotic drugs were risperidone (n = 144), haloperidol (n = 72), olanzapine (n = 60), quetiapine (n = 21), and aripiprazole (n = 21). One hundred twenty-five subjects (31.1%) were receiving antipsychotic polypharmacy. Antiepileptic drugs, lithium, anticholinergics, and antihypertensives were used in 92, 32, 281, and 74 subjects, respectively.

A preliminary analysis showed that any of the use of antiepileptic drugs, lithium, anticholinergics, or antihypertensives was not found to have any significant effect on the range of postural sway (all P's > 0.05) (corrected model: $F_{75,326} = 1.54$, $P = 0.06$, $R^2 = 0.26$), and these variables were excluded in the following main analysis. A univariate general linear model showed significant effects of class of antipsychotic drugs

TABLE 3. Range of Postural Sway in the Total Sample and a Subgroup of Subjects Without EPSs

Characteristics	Total Sample (n = 402)	EPSs (−) (n = 300)
Main antipsychotic drug		
Antipsychotics with a CPZE of <10	5.1 (4.9)	4.8 (4.7)
Antipsychotic with a CPZE of ≥10	7.1 (16.5)	7.8 (19.1)
BMI, kg/m^2		
<18.5	5.2 (4.1)	5.2 (4.0)
18.5–25.0	5.2 (4.9)	4.8 (4.7)
>25.0	5.7 (11.1)	5.8 (12.4)
Treatment setting		
Inpatient	3.7 (3.3)	3.4 (2.4)
Outpatient	5.7 (7.9)	5.5 (8.6)
Age, y		
<50	4.8 (10.1)	4.9 (11.2)
≥50	5.7 (5.0)	5.4 (4.8)

Raw values are presented in cm^2 as mean (SD).

A univariate general linear model showed significant effects of main antipsychotic drugs ($F_{1,385} = 8.26$, $P = 0.04$), BMI ($F_{2,385} = 11.23$, $P < 0.001$), and treatment settings ($F_{1,385} = 4.94$, $P = 0.027$) on the range of postural sway (corrected model: $F_{16,385} = 4.04$, $P < 0.001$, $R^2 = 0.14$), whereas age groups were found to have a trend-level effect ($F_{1,385} = 3.51$, $P = 0.06$). Another univariate general linear model showed significant effects of main antipsychotic drugs ($F_{1,285} = 7.89$, $P = 0.005$), BMI ($F_{2,285} = 14.06$, $P < 0.001$), treatment settings ($F_{1,285} = 4.76$, $P = 0.030$), and age groups ($F_{1,284} = 19.33$, $P < 0.001$) on the range in a subgroup of subjects who did not show EPSs (corrected model: $F_{14,285} = 5.23$, $P < 0.001$, $R^2 = 0.20$).

(ie, CPZE: ≥10 or <10) ($F_{1,385} = 8.26$, $P = 0.04$), BMI ($F_{2,385} = 11.23$, $P < 0.001$), treatment settings ($F_{1,385} = 4.94$, $P = 0.027$), and the interaction term of age groups and BMI ($F_{2,385} = 8.46$, $P < 0.001$) on the range of postural sway (corrected model: $F_{16,385} = 4.04$, $P < 0.001$, $R^2 = 0.14$), whereas age groups were found to have a trend-level effect ($F_{1,385} = 3.51$, $P = 0.06$). The observed values of the range of postural sway were numerically greater in subjects receiving antipsychotics with a CPZE of 10 or greater, the high BMI group, and inpatients (Table 3). The use of benzodiazepines and antipsychotic dose were not found to have any effects on the range in our sample. To exclude effects of EPSs on postural sway, another general linear model was created for a subgroup of subjects who did not present any EPSs (n = 300). This additional analysis not only consolidated the findings in the total sample, but also revealed a significant effect of age groups ($F_{1,285} = 22.91$, $P < 0.001$) on the range of postural sway (corrected model: $F_{14,285}$, $P < 0.001$, $R^2 = 0.20$) (Table 3); older subjects showed a greater degree of postural sway.

To evaluate the effects of individual atypical antipsychotic drugs on the postural sway, another analysis was performed in a subgroup of subjects who received those drugs (n = 246); this model demonstrated effects of drugs where quetiapine was associated with a greater degree of postural instability ($F_{3,222} = 2.93$, $P = 0.034$; corrected model: $F_{23,222} = 2.54$, $P < 0.001$, $R^2 = 0.21$) (Fig. 1). These findings were also replicated in patients who were receiving atypical antipsychotics and did not present EPSs (n = 178) ($F_{3,154} = 4.52$, $P = 0.005$; corrected model: $F_{23,154} = 8.12$, $P < 0.001$, $R^2 = 0.55$) (Fig. 1).

The range of postural sway in schizophrenia patients included in the present study was contrasted to those in control subjects, using the reference data (Figs. 2 and 3). These data were obtained, using the same methodology from 618 men and 871 women.[19] Although any statistical comparisons were not feasible, schizophrenia patients generally showed a greater degree of postural sway, compared with healthy people, irrespective of sex and age.

DISCUSSION

To our knowledge, this is the largest study that has examined postural sway in patients with schizophrenia and identified demographic and clinical characteristics that influenced postural

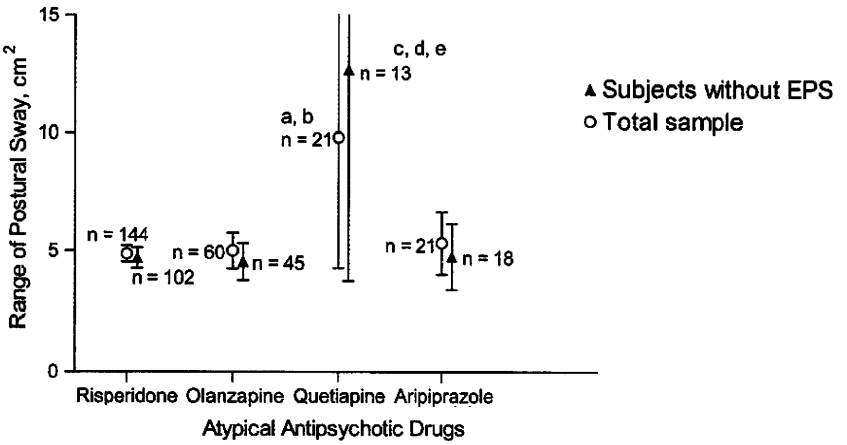

FIGURE 1. Range of postural sway in subjects who were receiving 4 atypical antipsychotic drugs. Open squares and closed circles indicate raw mean ranges of postural sway in all subjects who were receiving atypical antipsychotic drugs, and those who did not present EPSs, respectively. The vertical bars represent SEs. The mean values for quetiapine were 9.8 (SD, 5.5) for the total sample and 12.7 (SD, 8.9) for subjects without EPSs. General linear models demonstrated effects of drugs on the range of postural sway in all subjects who were receiving atypical antipsychotic drugs ($F_{3,222} = 2.93$, $P = 0.034$; corrected model: $F_{23,222} = 2.54$, $P < 0.001$, $R^2 = 0.21$) and those who did not present EPSs ($F_{3,154} = 4.52$, $P = 0.005$; corrected model: $F_{23,154} = 8.12$, $P < 0.001$, $R^2 = 0.55$), respectively. [a]$P = 0.048$ by the Tukey-Kramer HSD versus risperidone, [b]$P = 0.093$ by the Tukey-Kramer HSD versus olanzapine, [c]$P = 0.001$ by the Tukey-Kramer HSD versus risperidone, [d]$P = 0.002$ by the Tukey-Kramer HSD versus olanzapine, [e]$P = 0.013$ by the Tukey-Kramer HSD versus aripiprazole.