Neuropsychiatric Disease and Treatment

(South African Excerpts Edition)

VOLUME 8 · NUMBER 2 · 2014

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Neuropsychiatric Disease and Treatment

(South African Excerpts Edition)

EDITORIAL

This edition of the journal contains four articles, three of which are reviews, and one article reports on original research.

Two articles concern schizophrenia. The article by Williams *et al*, report on original research from the Canadian arm of the e-STAR project. This study was funded by Janssen Inc, the producer of Risperidone Long-Acting Injection (RLAI). The article reports on a 24-month naturalistic follow-up study of patients initiated on RLAI. The research compared a 12-month retrospective period for each participant with the 24-month prospective study period and reported on adherence, symptom-reduction, hospitalisation rates and global improvement in functioning. There was a 35% loss-to-follow up during the course of the study, but participants on RLAI for any length of time showed marked reductions in clinical symptoms and re-hospitalisation rates, with those who remained on treatment for the full study period having the best outcomes.

Gonzalez *et al* reviewed literature on unmet needs in schizophrenia. Their review covers a range of aspects of unmet need, including access to psychiatric care, prevention and management of the high-risk medical conditions that occur in people with schizophrenia, management of dual-diagnosis (substance use disorders and schizophrenia, as well as comorbid psychiatric disorders) as well as psychosocial and human rights unmet needs. The review suggests that there are significant unmet needs in people with schizophrenia, even in well-resourced countries. The article highlights the essential need for effective medication to treat schizophrenia, but also the essential need for a comprehensive approach to the management of schizophrenia, including good medical care, assertive community care, psychosocial and rehabilitation services.

Sung *et al* have provided a review of drugs used in the management of Autism Spectrum Disorders. They briefly provide information on drugs used to treat behaviour problems in ASD as well as comorbidities (ADHD, anxiety and depressive disorders), but the main focus of the review is on novel treatments for core features of ASD. These include melatonin, omega-3-fatty acids, memantine and oxytocin. Some of these medications show promising results for this disabling condition.

Vortioxetine is a new antidepressant, which has not yet been launched in South Africa. This review by Catona *et al*, who has been involved in a sponsor-driven clinical trial of vortioxetine, outlines preclinical and clinical data on this antidepressant, which has multimodal effects on the serotonergic system. The results of clinical trials conducted thus far seem to indicate that it is more effective than placebo, and equivalent to other antidepressants, although most studies reported show combination serotonergic-noradrenergic (SNRI) antidepressants are more effective. There is some suggestion that vortioxetine exerts a beneficial effect on memory and other cognitive functions in patients with depressive disorders. It appears to have a favourable side-effect profile.

Adjunct Professor RGM Thom, Division of Psychiatry, Faculty of Health Sciences, University of the Witwatersrand

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ORIGINAL RESEARCH

REVIEW

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ORIGINAL RESEARCH

Risperidone long-acting injection in the treatment of schizophrenia: 24-month results from the electronic Schizophrenia Treatment Adherence Registry in Canada

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Linda Beauclair[3]
Doanh Luong[4]
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On behalf of the e-STAR study group

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Objective: To assess outcomes over 24 months in Canadian patients with schizophrenia initiated on risperidone long-acting injection (RLAI) and participating in the electronic Schizophrenia Treatment Adherence Registry (e-STAR).

Materials and methods: Patients with schizophrenia or schizoaffective disorder were enrolled from 24 sites after an independent decision to initiate RLAI. Subsequent patient management was based on usual clinical practice at each site and was not protocol-driven. Relevant data were collected retrospectively by chart review for 12 months prior to RLAI and prospectively for 24 months following RLAI initiation.

Results: Patients (n=188) had a mean age of 39.2 years, were 66.3% male, and 27.7% were inpatients at baseline. Twenty-four months after initiating therapy (initial dose =28.7 mg), 34.1% (95% confidence interval 27.2%–42.2%) of patients had discontinued RLAI with a mean time to discontinuation of 273.4±196 days. Over the treatment period, there were significant ($P<0.001$) changes from baseline in Clinical Global Impression-Severity (CGI-S; 3.48 versus [vs] 4.31 at baseline), Global Assessment of Functioning (GAF; 56.1 vs 48.1), and Personal and Social Performance (PSP; 59.1 vs 46.9) scale scores. In addition, after 12 months, there were significant ($P<0.001$) decreases in the percentage of patients hospitalized (23.9% vs 58.5% pre-RLAI), mean length of stay (11.4 vs 30.4 days), and number of hospitalizations (0.32 vs 0.87) compared to the 12-month pre-RLAI period. Reductions in hospitalization continued into the second 12 months of therapy, when only 9% of patients were hospitalized and mean length of stay was 2.0 days.

Conclusion: In a routine clinical practice setting, patients switched to RLAI showed significant improvements in clinical outcomes and in global and social functioning, and hospitalization was significantly reduced. The data confirm that RLAI provides effective long-term management of schizophrenia in Canada.

Keywords: schizophrenia, Canada, risperidone long-acting injection, e-STAR

Introduction

Antipsychotic depot formulations offer a potential solution to poor oral medication adherence in patients with schizophrenia.[1] Nonadherence and partial adherence to therapy are common in patients on oral antipsychotic therapy, resulting in poor symptom control and increased rates of relapse and hospitalization.[2–4] In addition to the negative clinical patient outcomes, increased hospitalizations due to relapse are a major contributing factor in the overall treatment costs of schizophrenia.[4–6] In

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Canada, the annual direct health care cost of schizophrenia was estimated at CAD$1,868 million in 2004, with 66% of this cost due to hospitalization, a major component of which can be attributed to disease relapse.[7] Depot formulations, administered through periodic injections, offer several clinical and therapeutic advantages over oral antipsychotics. They avoid potential problems associated with reliance on patients taking daily oral therapy, allow monitoring of patient compliance through regular clinic contact, provide more consistent plasma levels of antipsychotic drug between injections, and improve adherence to therapy.[8,9]

First-generation or typical depot antipsychotic formulations have been available since the 1960s, and have been used extensively in the maintenance treatment of schizophrenia.[10] Although these medications may offer a benefit to patients in terms of increased adherence to therapy, the evidence for reduction in relapse rates and hospitalization compared to oral drugs is inconsistent.[8,10] One of the limiting factors of first-generation oral and depot drugs is the relatively high incidence of extrapyramidal symptoms, including tardive dyskinesia.[8,11] These unpleasant side effects reduce the effective capacity of these depot and oral agents to control schizophrenia.[11]

Second-generation or atypical antipsychotics can be more efficacious, and are generally better tolerated than first-generation drugs.[12,13] However, long-term therapy with oral atypicals is still compromised by poor adherence.[3,13,14] Risperidone long-acting injection (RLAI) was the first atypical antipsychotic available in an injectable formulation, and its efficacy and tolerability have been demonstrated in clinical trials.[15–17] RLAI therefore offers the tolerability of a second-generation antipsychotic with the improved adherence of an injectable therapy. However, stringent patient-inclusion criteria and short study durations in clinical trials limit the ability of investigators to apply observations from such studies to antipsychotic use in real-world clinical practice.[18,19] Observational studies are frequently used to assess the impact of therapies in clinical practice, where recruited patients and their treatment are more reflective of the routine management of schizophrenia.[19,20] The electronic Schizophrenia Treatment Adherence Registry (e-STAR) was established to assess long-term outcomes in patients with schizophrenia initiating treatment with RLAI under real-world clinical practice conditions. Initial e-STAR data from numerous countries indicate that a switch to RLAI leads to significant improvements in clinical and functional outcomes, reduction in hospitalizations, and high levels of adherence to therapy in schizophrenia patients.[2,21–24] The present paper describes the results of the e-STAR study in Canada.

Materials and methods

Study design

The e-STAR study was an international, multicenter, non-interventional, observational registry designed to collect clinical outcomes in patients with schizophrenia initiating treatment with RLAI. The objective was to assess the effectiveness of RLAI on control of schizophrenia symptoms and to quantify the impact of treatment on hospitalization. The e-STAR methodology has been described by Olivares et al.[25] In brief, patients with schizophrenia were recruited across Canada and enrolled in e-STAR after the decision to initiate treatment with RLAI, or switch to RLAI from their current oral or depot antipsychotic regimen, was made by their physicians. At baseline, prior to initiation of RLAI, data on hospitalization history and medication usage were collected by retrospective chart review for a minimum period of 12 months. Following initiation of RLAI, prospective data were collected for 24 months at approximately 3-month intervals. This study reports on the outcomes for all patients participating in the e-STAR study in Canada after 24 months.

Study population

The study was conducted at 24 community mental health centers across Canada, and all participating psychiatrists were actively involved in the treatment of schizophrenia. Any male or female inpatient or outpatient who was being initiated or switched to RLAI, based on an independent decision by the treating physician, was eligible for inclusion in the e-STAR registry, with the exception of chronically hospitalized patients who had no possibility of being discharged over the 24-month observation period, patients with treatment-resistant schizophrenia, or patients who were pregnant or currently breastfeeding. In addition, patients with a contraindication to RLAI or those currently participating in a clinical trial were excluded. There were no study-mandated treatment choices once a patient was enrolled, and clinical management was determined solely by the treating psychiatrist. Participating investigators were instructed to treat patients with RLAI in accordance with the manufacturer's prescribing information, but initial drug doses and use of concomitant psychiatric medications were based on the physician's judgment. All recruited patients or their authorized legal representative provided written informed consent, and the study was approved

by appropriate local institutional review boards/independent ethics committees.

Data collection

As in other countries, e-STAR data were collected mainly through a secure web-based system that maintained patient and data confidentiality.[24] However, traditional paper-based data collection was also available. Data for patients enrolled in e-STAR were recorded at baseline and every 3 months for a total of 24 months following RLAI initiation, even if patients had discontinued RLAI and switched to an alternative therapy. At baseline, patient-demographic and disease-history data were collected, as well as the reason for switching to RLAI. In addition, Clinical Global Impression-Severity (CGI-S),[26] Global Assessment of Functioning (GAF),[27] and Personal and Social Performance (PSP)[28] scale scores were assessed by investigators. Retrospective chart review was used to collect data on hospitalization and overall medication use over a 12-month period prior to the initiation of RLAI.

Following initiation of RLAI, the patient returned to the clinic every 3 months (±2 weeks), when data on hospitalization, CGI-S, GAF, PSP, RLAI dosing changes, concomitant medication utilization, treatment discontinuation, and reasons for discontinuation were collected. In addition, at each visit, psychiatrists were asked to assess the patient's adherence to RLAI using a 5-point Likert scale, with scores ranging from 0 (never) to 4 (always). Every attempt was made to follow all patients for the full 24 months, even those who discontinued RLAI.

Statistical analysis

A sample-size analysis for the Canadian study was based on the difference in the number of days spent in hospital during the first year with RLAI compared to the 12 months prior to RLAI. In a previous study, the 12-month reduction in hospitalization with RLAI was 8.8±37.1 days.[29] Based on this estimate, a sample size of 189 patients (237 assuming a 20% dropout) would be required to show, with 90% power, a significant difference at α=0.05 using a two-sided paired *t*-test.

Kaplan–Meier survival curves were used to estimate time to all-cause RLAI discontinuation; patients who were still using RLAI at 24 months were censored. All models were fitted using a stepwise selection procedure, with inclusion and exclusion significance of 5%.[21] CGI-S, GAF, and PSP scores at baseline and each visit were expressed as mean scores, and the statistical significance of change in score from baseline was calculated using a paired *t*-test.

Hospitalization parameters over the retrospective period (pre-RLAI) were compared with the first and second 12-month RLAI treatment periods. Statistical significance of change in percentage of patients hospitalized, length of stay, and number of stays over 12 months pre- and post-RLAI were assessed using McNemar's test, paired *t*-test and signed-rank test, respectively. For those who were inpatients at the time of initiation of RLAI, the baseline date was assumed to be the date of discharge, ie, hospitalization was assumed to apply to the retrospective period, since this was related to prior antipsychotic therapy. All statistical analyses were carried out using SAS version 9.1 (SAS Institute, Cary, NC, USA).

Results

A total of 188 patients were recruited for the study from 24 sites across Canada. Patients had a mean age of 39.2 years, the majority were male (66.3%), and 27.7% were inpatients at initiation of RLAI (Table 1). At baseline, mean CGI-S score was 4.31, and 36.9% of the patients were categorized as having marked or severe disease. Mean scores for GAF and PSP were 48.1 and 46.9, respectively. The mean GAF baseline score indicated moderate-to-severe functional impairment,[27] and the PSP score categorized patients as having marked to very severe difficulties in two or more of the four PSP domains.[30]

Three months prior to the initiation of RLAI, the majority of patients (n=130 [69.1%]) were receiving an oral atypical (51.5% on risperidone, 41.5% on olanzapine) either alone (n=74 [39.4%]) or in combination with a conventional depot (n=44 [23.4%]) or a conventional oral antipsychotic (n=7 [3.7%]) or both (n=5 [2.7%]), while 31 patients (16.5%) were receiving no treatment (Table 1). In addition, before the switch to RLAI, 80.7% of the patients were receiving concomitant psychiatric medication (Table 1). The most common reasons for initiation of RLAI were poor compliance (28.7% of patients), insufficient response (28.2%) with prior antipsychotic medication, and unacceptable tolerability/adverse events (21.2%) (Table 1).

The mean RLAI dose at initiation of therapy was 28.7 mg, with 82.4%, 4.3%, and 12.8% of patients initiated on 25 mg, 37.5 mg, and 50 mg, respectively. RLAI dose increased over the treatment period, and at 24 months, mean dose was 39.9 mg (44.6% were receiving 50 mg RLAI versus [vs] 31.5% and 21.7% on 25 mg and 37.5 mg, respectively; data not shown). The mean time on RLAI for the 188 patients

Table 1 Baseline characteristics of patients

Characteristic	All patients (n=188)
Age, years, mean ± SD	39.2±13.7
Male, n (%)	124 (66.3%)
Inpatients at baseline, n (%)	52 (27.7%)
Years since diagnosis, mean ± SD	10.4±10.7
Diagnosis, n (%)	
Schizophrenia	143 (76.1%)
Schizoaffective disorder	36 (19.1%)
Other	9 (4.8%)
CGI-S, mean ± SD	4.31±1.06
GAF mean ± SD	48.1±12.2
PSP mean ± SD	46.9±16.0
Antipsychotic medication utilization (% of patients)[a]	
Oral atypical	39.4%
Oral conventional	1.1%
Oral atypical + conventional	3.7%
Conventional depot	11.2%
Oral antipsychotic + conventional depot	28.2%
None	16.5%
Other baseline psychiatric medication utilization (% of patients)[b]	
None	19.3%
Anticholinergic	32.6%
Antidepressant	33.2%
Mood stabilizer	27.3%
Benzodiazepine	39.0%
Somatic medications	44.4%
First reason for initiating RLAI (% of patients)	
Compliance	28.7%
Insufficient response	28.2%
Unacceptable tolerability/adverse events	21.2%
All other reasons[c]	21.3%
Not reported	0.5%

Notes: [a]Three months prior to the initiation of RLAI; [b]mean utilization over the 12 months prior to RLAI initiation; [c]all other reasons – convenience, maintenance, patient/family choice, and others.

Abbreviations: SD, standard deviation; RLAI, risperidone long-acting injection; CGI-S, Clinical Global Impression-Severity scale; GAF, Global Assessment of Functioning; PSP, Personal and Social Performance scale.

in the study was 15.92 months. Table 2 provides additional details on the utilization of RLAI and concomitant antipsychotics over the treatment period, and shows that at baseline 89.9% of patients initiated RLAI in combination with another antipsychotic. Over the treatment period, the proportion of patients receiving concomitant oral atypicals decreased (17% of patients were receiving RLAI and oral atypicals at 24 months, vs 60.6% at baseline) while the number receiving RLAI alone increased. At 24 months, of the 92 patients still using RLAI, 57.6% were on monotherapy.

Investigator-assessed levels of treatment adherence indicated that the proportion of patients always adherent increased from 88.5% at 3 months post-RLAI initiation (n=131) to 100% at 24 months (n=72). There were no significant differences in the proportion of patients receiving other psychiatric medications following initiation of RLAI, and the levels observed at baseline (Table 1) were similar to those seen at 24 months (data not shown).

As shown in Figure 1, the Kaplan–Meier analysis indicated that after 24 months, 34.1% (95% confidence interval [CI] 27.2%–42.2%) of the patients had discontinued RLAI therapy. The mean time to discontinuation was 273.4±196 days, with a median, minimum, and maximum of 229, 15, and 682 days, respectively. The major reasons for discontinuation were loss to follow-up (35.2%), insufficient response (22.2%), and patient/family choice (13.0%) (data not shown). Adverse events and unacceptable tolerability led to discontinuation of only five patients (9.3%).

Over the treatment period there were statistically significant changes in all effectiveness parameters assessed (Figure 2). After only 3 months, the mean CGI-S score decreased significantly from 4.31 at baseline to 3.95 (P=0.001), and this decrease continued over 24 months to 3.48 ($P<0.001$ compared to baseline), giving a reduction of 0.82 points. In addition, only 13.0% of patients were categorized as having marked or severe disease at 24 months (36.9% at baseline), while 50.7% had very mild/mild disease (20.9% at baseline) (results not shown). The rapidity of RLAI action on effectiveness parameters was also apparent in the GAF and PSP scores (Figure 2). GAF scores at 3 months increased significantly from baseline (53.0 versus 48.1, $P<0.001$), and showed further improvement at 24 months (56.1 at 24 months, $P<0.001$). For the PSP, the baseline score of 46.9 increased to 54.2 ($P<0.001$) and 59.1 ($P<0.001$) at 3 and 24 months, respectively, indicating rapid and sustained improvement in social functioning (Figure 2). There were no significant differences in baseline parameters (age, sex, CGI-S, GAF, and PSP scores, hospitalization at baseline, and diagnosis) between patients who did not discontinue RLAI and those who were lost to follow-up or discontinued. However, post hoc analysis indicated that with RLAI therapy, the latter patients were not improving as quickly as patients who continued RLAI therapy. For example, when change in CGI-S scores from baseline to 24 months was assessed separately for patients who continued RLAI and those who did not, change for the latter patients was 0.6 (CGI-S scores were 4.3 at baseline [n=52] vs 3.7 at 24 months [n=7]), compared to 1.0 for patients who continued (4.3 at baseline [n=136] vs 3.3 at 24 months [n=48]); results were similar for the two populations in GAF and PSP score changes from baseline.

RLAI also had a significant impact on hospitalization parameters (Table 3). Following initiation of RLAI, there was

Table 2 Antipsychotic drug utilization over the study period

Antipsychotic therapy	Baseline,[a] n (%) of patients	Post-RLAI switch, n (%) of patients		
		3 months	12 months	24 months
RLAI alone	19 (10.1%)	57 (30.3%)	51 (27.1%)	53 (28.2%)
RLAI + OA	114 (60.6%)	92 (48.9%)	60 (31.9%)	32 (17.0%)
RLAI + OC	3 (1.6%)	3 (1.6%)	3 (1.6%)	2 (1.1%)
RLAI + CD	11 (5.9%)	3 (1.6%)	0%	0%
RLAI + OA + OC	12 (6.4%)	10 (5.3%)	7 (3.7%)	4 (2.1%)
RLAI + OA + CD	25 (13.3%)	5 (2.7%)	1 (0.5%)	1 (0.5%)
RLAI + other	4 (2.1%)	1 (0.5%)	0%	0%
Lost to follow-up/no therapy	0%	13 (6.9%)	58 (30.9%)	86 (45.7%)

Notes: [a]Percentage data for each assessment are based on n=188; patients who switched from RLAI to OA, OC, or CD therapy (n=4, n=8, and n=10 at 3-, 6-, and 12-months, respectively) are excluded.

Abbreviations: RLAI, risperidone long-acting injection; OA, oral atypical; OC, oral conventional; CD, conventional depot.

a significant decrease in the percentage of patients hospitalized from 58.5% over the pre-RLAI period to 23.9% over the 12-month post-RLAI period ($P<0.001$). In addition, average length of stay decreased by 62.5% (30.4 to 11.4 days per patient, $P<0.001$) and the average number of stays decreased by 63.2% (0.87 to 0.32 per patient, $P<0.001$) (Table 3). The impact of RLAI continued into the second 12-month period, with further decreases in patients hospitalized (9.0%) and in the duration (2.0 days) and number of stays per patient (0.11 stays) (Table 3).

Discussion

The e-STAR study has consistently shown that RLAI is associated with high medication retention rates and clinical and functional improvements in schizophrenia patients in several countries, despite structural differences in health care-delivery systems and in the management of schizophrenia.[2,21–25] In addition, in all countries, RLAI therapy led to significant reductions in psychiatric-related hospitalization, a major contributing factor in the overall treatment costs of schizophrenia.[2,21–24] The results from the present study indicate a similar impact of RLAI on the treatment of patients with schizophrenia in Canada after a switch from prior therapy, which included oral first- and second-generation antipsychotics and typical depot antipsychotics. Over the 24 months of treatment, 65.9% of patients remained on RLAI therapy, and there were rapid and maintained significant improvements in clinical effectiveness and patient functioning, which were accompanied by significant decreases in hospitalization.

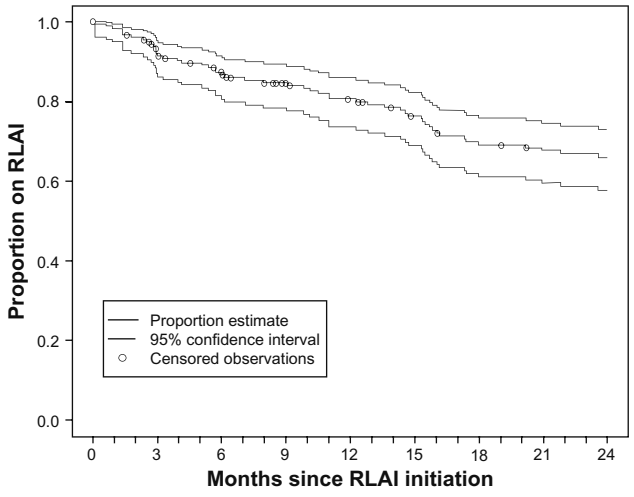

Figure 1 Kaplan–Meier estimate for the time to discontinuation of risperidone long-acting injection (RLAI). The mean time to discontinuation for the 54 patients (34.1%) who discontinued RLAI therapy before 24 months was 273.4±196 days.

The observed RLAI 24-month discontinuation rate in Canada (34.1%) was within the range of rates reported in other countries. The e-STAR study has reported variable 24-month discontinuation rates of 2.1%–49% in six European countries, with an overall rate of 15%.[22] Variation in RLAI discontinuation rates across countries likely reflects differences in clinical practice patterns, variable patient disease severity, and RLAI dosing strategies.[22] One of the major reasons for RLAI discontinuation in the present study was loss to follow-up; 19 patients (35.2% of discontinued patients) discontinued therapy for this reason, likely a reflection of the observational nature of the study design. In the absence of this extensive loss to follow-up, Canadian discontinuation rates may have been much lower. Although oral atypicals were not assessed in the present study, previous naturalistic studies have suggested that retention rates with RLAI in patient populations with similar disease severity are superior to rates in patients receiving oral therapy.[21,31] In a prior Canadian retrospective chart-review study, over 3 years 50.5% (95% CI 41.9%–62.1%) of patients initiated on an oral atypical switched medication, compared to only 39.1% (95% CI 28.8%–51.7%) initiated on RLAI.[31] These naturalistic studies provide consistent real-world evidence

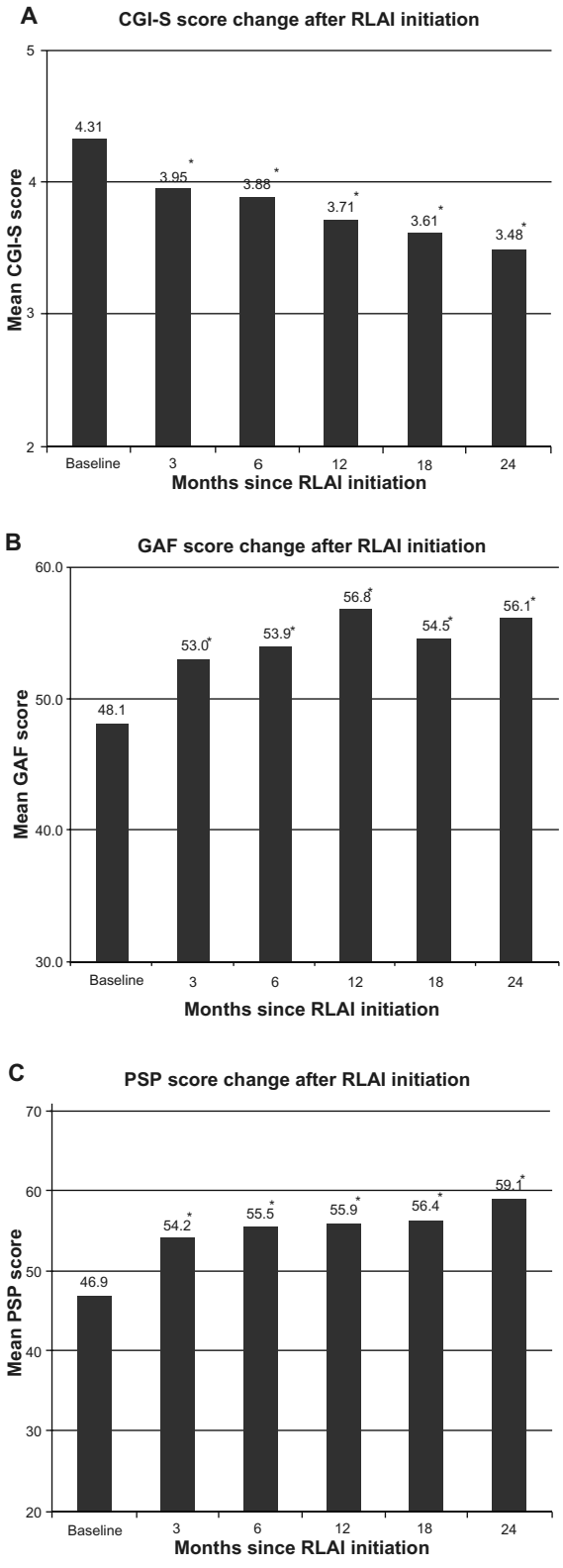

Figure 2 Change in Clinical Global Impression-Severity (CGI-S) (**A**), Global Assessment of Functioning (GAF) (**B**), and Personal and Social Performance (PSP) (**C**) scale scores from baseline following a switch to risperidone long-acting injection (RLAI). Scores are expressed as mean values based on patients with data at each assessment point.

Notes: *Statistically significant change from baseline. $P<0.001$ for all time points, except for CGI-S at 3 months, where *P*-value was 0.001. All *P*-values were associated with the hypothesis of no difference from baseline (paired *t*-test).

Table 3 Impact of RLAI on hospitalization parameters (n=188)[a]

Hospitalization	Pre-RLAI (12 months)	Post-RLAI	
		0–12 months	12–24 months
Patients hospitalized, n (%)	110 (58.5%)	45 (23.9%)[b]	17 (9.0%)
Length of stay, days (mean ± SD) per patient	30.4±58.4	11.4±35.7[c]	2.0±9.2
Number of stays (mean ± SD) per patient	0.87±0.96	0.32±0.62[d]	0.11±0.37

Notes: [a]Analysis based on the assumption that for inpatients at initiation of RLAI (n=52 [27.7%]) baseline date for the post-RLAI assessment was their discharge date; [b]statistically significant change compared to the 12-month pre-RLAI period ($P<0.001$), *P*-value associated with the hypothesis of no difference between the retrospective and prospective periods (McNemar's test); [c]statistically significant change compared to the 12-month pre-RLAI period ($P<0.001$), *P*-value calculated using paired *t*-test; [d]statistically significant change compared to the 12-month pre-RLAI period ($P<0.001$), *P*-value calculated using signed-rank test.

Abbreviations: RLAI, risperidone long-acting injection; SD, standard deviation.

that long-term adherence to RLAI therapy is high, and that this in turn is associated with significant impacts on symptom control in schizophrenia and reductions in disease-related hospitalization.[21,31]

RLAI treatment also led to significant changes in CGI-S scores, which decreased by 0.82 points over 24 months, and there was a 2.4-fold increase from baseline in the proportion of patients with very mild or mild disease after the switch to RLAI. These changes are of a similar magnitude to those reported in previous studies (decreases ranged from 0.6 to 0.87 points)[21] after schizophrenia patients were switched to RLAI, and reflect the effectiveness of this second-generation injectable antipsychotic in controlling symptoms of schizophrenia.[2,21,25] The CGI-S improvements were not due solely to poor-outcome patients discontinuing or being lost to follow-up. All patients showed CGI-S improvement with RLAI therapy, but patients who did not discontinue had a faster and greater CGI-S decrease than patients who discontinued or were lost to follow-up. A similar difference in CGI-S score changes in RLAI continuers and discontinuers has been reported by Peuskens et al.[22] There were also significant changes in measures of global and social functioning, with increases in mean scores of 8.0 and 12.2 points on the GAF and PSP scales, respectively, after the switch to RLAI. There is increasing interest in social functioning in schizophrenia and a recognition that in addition to symptom control, treatment goals should include improvement in functional outcomes to facilitate reintegration of patients into society.[32,33] In schizophrenia patients, a change of ≥7 points on the PSP scale has been defined as a clinically meaningful change

in social functioning.[30,32] On this basis, the mean change of 12.2 points on the PSP 24 months after initiation of RLAI would indicate a clinically meaningful change in social functioning in patients treated in this study. Furthermore, this increase occurred rapidly after initiation of RLAI; of the total change in PSP score, 59.8% was apparent 3 months after the medication switch. The positive impact on patient functioning was also apparent in the significant change in GAF score over 24 months, 61.3% of which was apparent at 3 months. Apiquian et al[23] have also recently reported a rapid and significant change in PSP after schizophrenia patients were switched to RLAI. These data suggest that in addition to rapid improvement in schizophrenia symptoms, RLAI may also be effective in improving social functioning, evidence of a broad impact on both clinical and psychosocial aspects of schizophrenia.

Consistent with evidence from earlier observational studies,[2,21–23] the e-STAR data from Canada showed that over 12 months post-RLAI, 59.1% fewer patients were hospitalized compared to the pre-RLAI period ($P<0.001$), and there were significant ($P<0.001$) reductions in mean length of stay (62.5% reduction) and the number of hospitalizations (63.2% reduction). As in previous studies,[21,22] the decreases in hospitalization parameters were stable and continued into the second year of therapy. These data also confirm an earlier retrospective chart-review study of schizophrenia patients in Canada, which showed significant decreases in hospitalization when patients were switched to RLAI; in contrast, similar patients maintained on oral atypicals had an increased risk of hospitalization (95% CI defining risk of hospitalization was 54.7%–76.4% for oral atypicals over 3 years vs 1.8%–16.5% for RLAI).[31] These data indicate that in Canada, as in other countries,[21–23] a switch to RLAI from current antipsychotic therapy is associated with significant decreases in patient hospitalization, which could lead to considerable schizophrenia-related cost savings.[5,7,31] Potential cost savings of such a strategy have been quantified in Spain, where total per-patient monthly schizophrenia-treatment costs (including drug costs) over 24 months decreased by 22% after a switch to RLAI compared to a similar pre-RLAI period.[25] Similarly, in 2005, Chue et al[5] used a discrete-event simulation model to show that over 5 years, treatment of high-risk noncompliant schizophrenia patients in Canada with RLAI would generate assumed discounted savings of $13,130 per patient compared to treatment with oral risperidone. The present study demonstrates that in Canada, the long-term impact of RLAI on hospitalization is dramatic, and potentially provides Canadian-specific data for a more accurate assessment of the overall economic impact of RLAI utilization in this country.

There are a number of limitations associated with the present study design, which have been discussed in previous e-STAR publications.[2,21,22,24,25] An important limitation is that this was an observational study with loosely defined inclusion criteria and no comparator group, and thus lacks the validity of a randomized controlled trial. However, the value of the latter type of study on schizophrenia has been questioned because of selective patient recruitment, the short duration of studies, and protocol-driven procedures that may artificially enhance medication adherence to levels higher than those observed in clinical practice.[19,21] Therefore, large-scale, long-term, observational studies such as e-STAR can provide valuable information on schizophrenia outcomes.[19–21] An additional limitation is that part of the collection of data on hospitalization relied on retrospective chart review, and was dependent on the consistent recording of data on charts at all sites. Variation in the quality of data recorded may have affected the validity of the retrospective data. However, this is unlikely to have specifically impacted the Canadian data, since virtually all mirror-image-type studies to date have shown significant reductions in hospitalization after a switch to RLAI using similar retrospective chart-review procedures.[2,21–23]

Finally, the PSP used in this study required psychiatrists to rate patients' functioning status.[30] Although psychiatrists were trained to use the PSP, there was no information provided as to how they were to assess relevant patient-related parameters, which formed the basis of their ratings. Therefore, source data for the PSP ratings may have varied from site to site, potentially limiting the validity of the overall PSP scores.

At the time the e-STAR study was initiated, RLAI was the only atypical injectable antipsychotic available in Canada. Another second-generation antipsychotic, paliperidone palmitate, has since been approved for the treatment of schizophrenia in Canada, expanding therapeutic options for depot therapy.[34] This depot antipsychotic is the palmitate ester of paliperidone, the major metabolite of risperidone, and requires once-monthly injection.[35] While the e-STAR study has demonstrated the effectiveness of RLAI in real clinical practice, the long-term comparative effectiveness of paliperidone palmitate and RLAI in a similar clinical environment has not been addressed. However, a short-term (13 weeks) randomized, double-blind clinical trial has demonstrated equivalent efficacy and safety of RLAI and paliperidone palmitate in the treatment of schizophrenia.[35]

The present study design lays the groundwork for potentially similar studies with paliperidone palmitate, or any future depot antipsychotic, providing an effective way to address the use of these important drugs in clinical practice.

Conclusion

The present study demonstrates that in a real-world clinical practice setting in Canada, patients with schizophrenia switched from their current antipsychotic therapy to RLAI showed significant, rapid, and sustained improvements in clinical outcomes and in global and social functioning over 24 months. In addition, there were significant decreases in hospitalization over the same period. The data indicate that RLAI is an effective, injectable, second-generation antipsychotic, and that in addition to clinical and functional improvement, its use could result in considerable cost savings through reduced schizophrenia-related hospitalization.

Acknowledgments

Funding for this study was provided by Janssen Inc. The authors would like to acknowledge the e-STAR investigators in Canada who contributed patient data for this study. The authors would also like to thank John I McCormick, PhD, McKesson Specialty, Toronto, Canada who provided medical writing services, which were funded by Janssen Inc., Canada.

Disclosure

RW and RC have received speaking honoraria from Janssen Inc. and RC has also participated in Advisory Board meetings for Janssen Inc. RW, RC, and LB received grants to carry out the e-STAR study from Janssen Inc. DL and AL are employees of Janssen Inc. The authors report no other conflicts of interest in this work.

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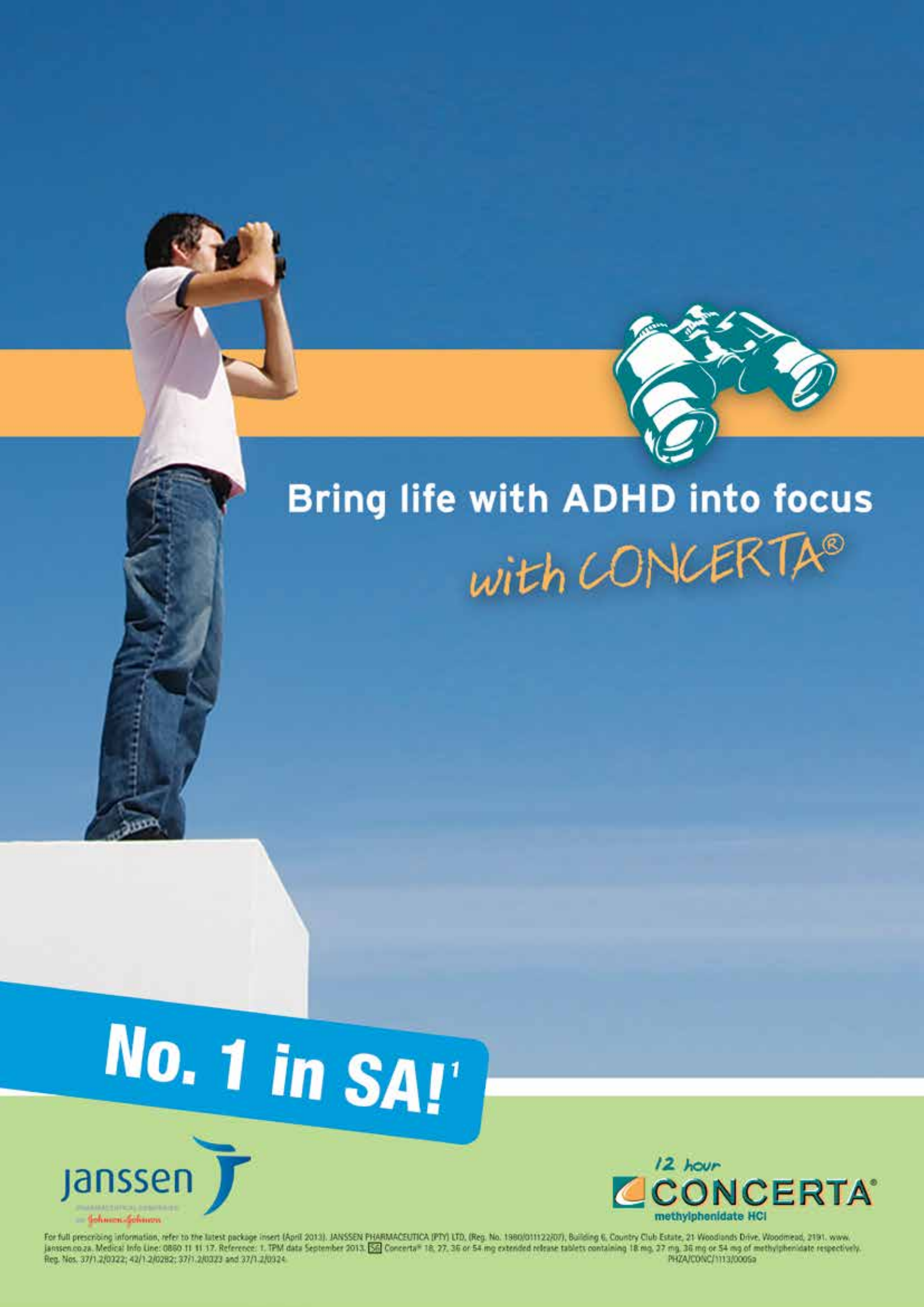

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REVIEW

What's in the pipeline? Drugs in development for autism spectrum disorder

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Abstract: Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder with both core symptoms and associated symptoms (eg, irritability, aggression, and comorbidities) that affect both the individual and the family/systems around them. There have been recent advances in the understanding of the underlying pathophysiology of ASD pertaining to genetics, epigenetics, neurological, hormonal, and environmental factors that contribute to the difficulties found in individuals with ASD. With this improved understanding, there has been a shift in the application of psychopharmacology in ASD and its related disorders. A literature review was conducted to examine research published in the last 5 years between different classes of psychotropic medications and ASD. The broad scope of the existing literature for the use of conventional medications is summarized and novel medications are discussed.

Keywords: pharmacology, treatment, autism, Asperger's syndrome, medication

Introduction

Autism Spectrum Disorder (ASD) is a complex disorder presenting with deficits in social interaction, social communication, and restricted, repetitive patterns of behaviors, interests, or activities. Currently, the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), and the International Statistical Classification of Diseases and Related Health Problems–10th Revision (ICD-10), are the dominant diagnostic classifications for this disorder. Pervasive Developmental Disorder – Not Otherwise Specified, as a category, remains less stable with higher degrees of variability in diagnosis within categorical and psychodynamic systems.[1] The recently developed DSM-5 has reconceptualized the spectrum into a broad category – ASD and Social Communication Disorder.[2] The diagnostic criteria for autism and its related disorders have been collapsed to encompass social communication and social interaction deficits as one criteria and restricted, repetitive patterns of behaviors, interests, and activities as the other. However, controversies remain with regards to categorization and diagnosis. This highlights the heterogeneity of the condition and the broader syndrome that we are considering when we examine literature on ASD.

ASD research continues to receive considerable attention as the options for successful management are limited. The understanding of the ASD etiology has now progressed to encompass genetic, epigenetics, neurological, hormonal, and environmental factors that affect outcomes for patients with ASD.[3] With the increasing diversity of basic sciences and publications relating to pharmacological options for patients with ASD, a review of recent literature about the treatment advances in this field is warranted. The application of medication in patients with ASD has traditionally targeted associated

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http://dx.doi.org/10.2147/NDT.S39516

conditions (such as inattention or irritability) that occur in the context of ASD, with poor evidence for the core symptoms of the condition. However, there are problems with the efficacy of medications in this population. In addition, children and young people with ASD also have a higher likelihood of developing intolerable side effects from the use of medications. Nevertheless, recent work has broadened the understanding of pharmacological use with newer medications being tried and studied in this population.

Electronic literature searches were conducted from the following sources: MedLine, the Cochrane Library, PsycARTICLES, and PsycINFO. Search terms included, but were not limited to, psychotropic medications (antidepressants, antipsychotics, mood stabilizers, melatonin, glutamate agonists, oxytocin, and attention deficit hyperactivity disorder (ADHD) medications (methylphenidate [MPH] and atomoxetine) autism, pervasive developmental disorders, ASD, and Asperger's syndrome from 2008 to 2013 (the last 5 years). The article abstracts obtained from the search strategy were perused and eligible articles were then retrieved. This article reviews recent evidence supporting various medications used in ASD. Evidence from trials published prior to 2008 was summarized to provide relevant background information.

Scope of medications covered

Conventional pharmacological management in ASD has targeted dysfunctional behavioral symptoms that interfere with rehabilitative efforts and cause impairment or distress, such as aggression, irritability, stereotyped behaviors, anxiety, hyperactivity, and sleep difficulties.[4] These pharmacological agents include the antipsychotics, antidepressants, mood stabilizers, and medications targeting inattention and hyperactivity. Conventional treatments, with limited recent literature, have been summarized to provide an overview and will be covered briefly. The focus of this article will be on novel treatments with recent interest, including melatonin, omega-3 fatty acids, glutamate receptor related medications, and oxytocin. These will be described in greater detail.

Antipsychotics

Antipsychotics are the most-studied class of medications in the ASD population for efficacy and effectiveness.

Haloperidol has previously been well-studied for efficacy and safety.[5] However, with concerns of extrapyramidal symptoms (EPS),[6] typical antipsychotics have been dropped in favor of atypical antipsychotics, which have emerged as the first-line pharmacologic treatment for behavioral problems in ASD.[7] As such, recent research in antipsychotic use in ASD has been limited to atypical antipsychotics.

While some atypical antipsychotics (such as risperidone and aripiprazole) have been better researched, others (such as olanzapine, quetiapine, and ziprasidone) have had limited data, with a few earlier case studies, open-label studies, or small double-blind placebo-controlled studies.[8–15] No recent studies have focused on these drugs. Concerns with regards to adverse effects (such as metabolic side effects) may have resulted in limited use.[5,7,16]

Risperidone is a US Food and Drug Administration (FDA) approved antipsychotic for the treatment of symptoms in children and adolescents with ASD.[7,17] Risperidone is useful in the management of behavioral problems, such as irritability, aggression, self-injurious behavior, hyperactivity, and repetitive behavior.[18–21]

Recent studies continue to demonstrate the efficacy of risperidone,[22–24] and focus on its safety and side effects. The most common adverse effects are weight gain, increased appetite, and somnolence.[22–25] Weight gain is a common problem and can cause significant health problems,[22] while somnolence may more significantly affect treatment discontinuation.[23] These side effects are more likely to occur in higher doses.[24]

There is interest in the combination of risperidone with other agents. For example, a small randomized controlled trial (RCT) showed that adding topiramate to risperidone was superior to risperidone alone in reducing irritability, stereotypic behavior, and hyperactivity.[26] In similar RCTs, there was reported benefit in adding pentoxifylline,[27] memantine,[28] and celecoxib[29] to risperidone in behavior problems. However, these results have not been verified in any other study.

Aripiprazole is the other FDA-approved atypical antipsychotic for use with children and adolescents with ASD.[30,31] There have been two RCTs demonstrating the efficacy of aripiprazole in reducing irritability, hyperactivity, and stereotypies.[32–34] The effect on irritability was sustained in an open-label follow-up trial of the above studies.[35] Efficacy has also been demonstrated in another recent open-label[36] study and a retrospective study.[37] However, aripiprazole is not without side effects, which includes weight gain, sedation, sialorrhea, and EPS.[30–34]

There are only case reports documenting the use of clozapine in children and adolescents with ASD. Only one case report was published recently, on a 15-year-old girl with ASD, who previously failed treatment with risperidone and haloperidol. Her aggressive behavior dramatically improved

with clozapine.[38] However, the risk of agranulocytosis limits the use of clozapine.

Paliperidone, the active metabolite of risperidone, has been found to be generally well-tolerated and effective in the treatment in adolescents and young adults with ASD, but more research is still needed. It may have an advantage over risperidone in children with hepatic impairment, but paliperidone still shares a similar adverse effect profile as risperidone.[17] Currently, published studies on the use of paliperidone in ASD are limited to an open-label trial[39] and a few case reports.[40,41] According to a recent open-label trial, side effects included weight gain, increased appetite, tiredness, EPS, and increased serum prolactin. In another case report, a 5-year-old boy with autism and severe aversion to oral medication was successfully treated with paliperidone palmitate given intramuscularly.[41]

There have been no recent published studies on the use of asenapine, sertindole, iloperidone, or amisulpride.

Antidepressants

Previous trials have suggested that children and adolescents with ASD showed improvements with fluoxetine.[42,43] More recently, a double-blind placebo-controlled trial with fluoxetine in adult patients reported significant improvement in their obsessive-compulsive symptoms and overall symptoms.[44] Although older trials did not find fluvoxamine to be effective in younger patients with ASD, a randomized double-blind placebo-controlled crossover study reported that fluvoxamine was helpful in treating young patients, and found response to be related to polymorphism within a serotonin transporter gene.[45] Improvements in anxiety, mood, and irritability have been suggested in studies on citalopram[46] and escitalopram.[47]

In a recent meta-analysis of both published and unpublished randomized double-blind placebo-controlled trials examining the use of selective serotonin reuptake inhibitor (SSRI) in ASD, Carrasco et al[48] reported a significant publication bias (ie, trials with positive results were more likely to be published). They found that although there was a significant treatment effect of SSRI (used for treating repetitive behaviors in ASD), these findings did not persist after they statistically adjusted for the publication bias. Meta-regression did not demonstrate a significant effect of SSRI treatment with age, although the trend among trials revealed that increased average patient age was associated with a greater treatment effect.[48] A Cochrane review examined RCTs that studied the efficacy of several SSRIs (fluoxetine, fluvoxamine, fenfluramine, and citalopram) in treating ASD and reported that there was no evidence that SSRIs improved ASD symptoms, adding that it may even possibly cause harm.[49]

Clomipramine, with its SSRI properties and efficacy in treating obsessive compulsive disorder (OCD), is the most-studied tricyclic antidepressant. Previous double-blind trials suggested that clomipramine improved ASD symptoms, anger outbursts, repetitive behavior, hyperactivity, and irritability.[50,51] In a Cochrane review on the efficacy of tricyclic antidepressants in treating ASD, three RCTs were examined.[52] Clomipramine appeared to improve ASD symptoms, irritability, and OCD-type symptoms, but its effect on hyperactivity was not consistent.

Overall, the role of antidepressants remains unclear, and more research is needed. Children and adolescents with ASD appear to experience significant side effects, such as behavioral activation (hyperactivity and agitation), aggression, and suicidal ideation,[53] all of which can limit its use.

Mood stabilizers/antiepileptics

A study found that divalproex was helpful for symptoms of irritability/aggression in children and adolescents with ASD,[54] while findings in earlier studies were inconsistent.[55,56]

Findings on levetiracetam have been inconsistent, with an open-label study showing improved symptoms of aggression, impulsivity, hyperkinesis, and mood instability,[57] while another, more recent placebo-controlled study reported no improvement in the behavioral problems associated with ASD.[58]

There have been no other recent positive findings for this class of medication and its use in ASD. However, it should be noted that this class of medication has significant side effects that limit its use in this population.

Medications for ADHD

MPH is a stimulant, which has been used in children with ASD and comorbid ADHD symptoms. However, its efficacy has been limited, due to the adverse side effects commonly reported in children with ASD, in comparison to children with ADHD alone.[59,60] An earlier review suggested that MPH was superior to the placebo, but the response rate was low, and the side effects were prominent in children with ASD.[61] This suggests that MPH is not as efficacious in ASD as it is for ADHD.

Recently, there has been a slight shift to what was previously found, as few studies have started to report positive results with MPH in children with ASD. A study of 20 preschool children aged 3–5 years old with developmental disorders showed an improvement in the parents' rating of ADHD symptoms, although adverse events were more

common.[62] Another recent study also reported positive results with MPH on social communication and self-regulation in children with ASD and hyperactivity.[63]

Although MPH has been associated with more adverse events in children with ASD, a number of trials suggested beneficial results in children with ASD.[65] Three RCTs have reported improvement of ADHD symptoms in children with ASD.[66–67]

Atomoxetine is a selective norepinephrine reuptake inhibitor, which is approved by the US FDA for the treatment of ADHD. It is a nonstimulant and, therefore, may offer better tolerability compared to MPH.[68] A recent review on atomoxetine suggested that its efficacy was most noticeable in individuals with a low severity of ASD.[69] Additionally, in a 10-week open-label study of 12 children with a high severity of ASD and symptoms of ADHD, results suggested that the participants did not benefit from atomoxetine and were more vulnerable to the adverse effects.[70] On the contrary, a number of studies have suggested beneficial results on ADHD symptoms with atomoxetine in children with ASD. A recent open-label study showed improvement in ADHD symptoms and fewer adverse effects in individuals with ASD who also met criteria for ADHD.[71] A recent double-blind placebo-controlled 8-week trial demonstrated the superior efficacy of atomoxetine compared to placebo on ADHD symptoms of children and adolescents with ASD. Additionally, improvements in ADHD symptoms were still observed after 28 weeks.[72] Several other studies have demonstrated improvements of ADHD symptoms with atomoxetine in children and adolescents with ASD.[73–76] In a 10-week open-label study, positive results with atomoxetine were also reported in high-functioning boys with ASD and comorbid ADHD.[77]

Guanfacine and clonidine (both alpha-2 adrenergic agonists) have been used in the treatment of ADHD. Contrary to clonidine, guanfacine has a longer half-life, which allows for lower dosing. In addition, it has fewer sedative effects. In earlier trials, guanfacine has been found to be effective in the ASD population in reducing hyperactivity, inattention, and impulsivity.[78–80] Clonidine is an FDA-approved medication, used as an adjunction medication in the traditional treatment of ADHD.[81] In previously published double-blind trials, clonidine was reported to reduce irritability, hyperactivity, and impulsivity.[82,83] However, the lack of current research in this area limits the conclusions that can be drawn for the use of clonidine in treating ASD.

Novel treatments

The quest to develop drugs to effectively target socialization and communication in ASD has been challenging. Factors contributing to this difficulty include the lack of specific understanding of the neurobiology of ASD, the heterogeneity of the condition, and the natural course of gradual improvement in these core symptoms over time. However, a number of drugs are beginning to show promise in the area and deserve further study.[84] Recent studies have also focused on medications traditionally regarded as complementary agents, suggesting potential benefits. These medications offer novel options to the practicing clinician in the management of the ASD population and, hence, have been presented in more detail.

Melatonin

An endogenous neurohormone, melatonin is secreted by the pineal gland, causing drowsiness. Melatonin levels increase rapidly after nightfall, peak in the middle of the night, and decrease toward dawn. Melatonin has been increasingly used to manage sleep disorders in children with ASD. In the last 5 years, various retrospective studies, open-label trials, and placebo-controlled trials have been conducted.

In a retrospective study on 107 children (aged 2–18 years old) with ASD, 85% of parents reported partial or full improvement in sleep.[85] Another case series studied six adults with ASD on melatonin retrospectively and reported improvements in long sleep latency, night waking, and settling difficulties.[86] A recent open-label trial[87] studied melatonin in 24 children with ASD over a 14-week intervention. Supplemental melatonin improved sleep latency in most children at 1 or 3 mg doses, within 1 week of treatment.

Small RCTs with melatonin have also shown promise. In a randomized, double-blind crossover trial in 18 children with ASD (n=8) and/or Fragile X syndrome, there was a significant increase in total sleep time and decrease in sleep latency in melatonin compared to placebo.[88] Another randomized, double-blind crossover trial was conducted on 22 children and adolescents with ASD involving 3 months of placebo and 3 months of melatonin. Melatonin significantly improved sleep latency and total sleep, and the side effect profile was low.[89] In addition, a randomized placebo-controlled trial examining insomnia in children with ASD was conducted. In their study, they compared melatonin alone, melatonin combined with cognitive behavioral therapy, cognitive-behavioral therapy and placebo in children with ASD.[90] Findings suggested that adding behavioral intervention to melatonin treatment, resulted in better treatment response, at least in the short term.

Melatonin appears to have potential in the treatment of sleep problems in ASD, although larger trials are needed.

Omega-3 fatty acids

A group of polyunsaturated fatty acids, the three main types found in the human diet are ALA (alpha-linolenic acid), DHA (docosahexaenoic acid), and EPA (eicosapentaenoic acid). DHA and EPA are found in seafood, while ALA is found in nut and plant oils. While the human body can synthesize both DHA and EPA from ALA, it cannot synthesize any of these fatty acids from scratch. Thus, these substances are called "essential fatty acids." Neural tissue contains high concentrations of DHA, and studies suggest that this fatty acid is essential to the growth and functional development of the brain.[91] Several studies have also reported low levels of omega-3 fatty acids in children with ASD compared to controls.[92] The RCTs of omega-3 supplementation have been conducted for the treatment of ADHD, depression, and schizophrenia.[93]

A recent Cochrane review was done on omega-3 fatty acids supplementation for ASD in 2011.[93] In the review, the authors highlighted two studies in which children who were diagnosed with ASD were randomized into groups that received either omega-3 fatty acid supplementation or a placebo. Overall, there was no evidence that the omega-3 supplementation had an effect on social interaction, communication, stereotypy, or hyperactivity. The largest positive effect for treatment was reported for hyperactivity. However, since the sample size was small, the findings may not have been sufficient to provide robust evidence. Larger clinical trials are currently ongoing, and the results would lend better clarity.

Glutamate receptor-related medications

Glutamate, the main excitatory neurotransmitter in our central nervous system, has been implicated in ASD. Glutamate is converted to gamma-amino butyric acid (GABA) in the brain by the glutamic acid decarboxylase protein. Related epigenetic factors involving GABA receptor genes have been associated with ASD.[94] Studies that have been initially performed suggest that GABA-signaling pathways are associated with stereotypies in a large proportion of experimental animal models for ASD, including Fragile X syndrome.[95–97] Similarly, there are reports suggesting associations between ASD and gene variations for glutamate receptors and glutamate transporter proteins.[98,99]

In one study in humans, the GABA type A receptors were found to be reduced in three brain sites which were possibly linked with the development of ASD, leading to the suggestion of extensive GABAergic dysfunctions in the brains of individuals with ASD.[100] The plasma levels of glutamate and glutamine were found to be high in children with high-functioning ASD,[101] leading to the postulation that the plasma levels of glutamate and glutamine could serve as early markers of glutamatergic dysfunction in ASD. In addition, an increased GABA level in the plasma of individuals with ASD has also been found.[102] In another study, an abnormality in the proportion of GABA to the glutamate level in the brains of individuals with ASD has also been suggested.[103] A recent review paper by Essa et al suggested that excessive glutamatergic activity might cause excitotoxicity in the brain that might result in the abnormal development of neurons leading to ASD.[104]

Various medications that work within the glutamatergic system, including at the N-methyl-D-aspartate (NMDA) subtype of the glutamate receptor, have been studied for their roles in treating ASD and the related symptoms. Glutamate antagonists work by blocking the glutamate receptor and moderating excessive excitation at the neuronal level. In one animal model, a glutamate antagonist, 2-methyl-6-(phenylethynyl)pyridine (MPEP) was studied in relation to autism. Although the authors have suggested that metabotropic glutamate receptor 5 (mGluR5) antagonism might be effective in the treatment of stereotypic behaviors, the MPEP might have adverse effects on the core symptoms of ASD (sociability). It was further postulated that the MPEP's effects appeared to be complex and inconsistent, which could have resulted in improvements in some aspects of sociability but worsening in others.[105,106] In a recently published animal model study using D-cycloserine, an NMDA-receptor agonist, the authors suggested that there were improvements in social behavior when used concurrently with social behavioral therapy. In addition, it was postulated that glutamate transmission might have a role in the development of social bonds in animals and that D-cycloserine enhances the assimilation of social information.[107]

Studies have also moved toward investigating glutamate receptor-related medications in clinical populations. In a double-blind clinical trial by Lemonnier et al, the diuretic, chloride-importer antagonist bumetanide, which reduces intracellular chloride and enhances GABAergic inhibition, was studied.[108] In this study, bumetanide showed significant improvements in the Childhood Autism Rating Scale, and Clinical Global Impressions and Autism Diagnostic Observation Schedule after eliminating the most severe cases. Side effects of mild hypokalemia were noted. As such, the authors went on to suggest that bumetanide could be a promising novel agent in treating ASD and highlighted the need for further extensive trials.

One of the more commonly known NMDA-receptor antagonists is memantine, which has been used in the treatment of Alzheimer's dementia. Memantine serves as a moderate affinity antagonist of the NMDA receptor. In a retrospective open-label study of 18 patients (6–19 years of age) with ASD, who were treated with memantine, eleven out of 18 responded with improvements in social withdrawal and inattention.[109] However, in the same study, seven out of 18 patients developed adverse effects, which included sedation, irritability, rash, emesis, and increased seizure frequency.

In another open-label study by Niederhofer, which studied the effects of memantine (20 mg per day for 4 weeks) in four children with ASD, the findings revealed significant improvements in irritability, hyperactivity, and inappropriate speech.[110] Similarly, an earlier study involving individuals with ASD showed improvements in the areas of hyperactivity, irritability, lethargy, and memory tests.[111]

Recently, there has been interest in the effects of combining memantine with risperidone. For example, in a 10-week, randomized double-blind, placebo-controlled trial, memantine combined with risperidone was prescribed to 40 children (4–12 years of age). The results demonstrated significant improvements in the memantine group in terms of irritability, stereotypic behavior, and hyperactivity. Such a combination was also well-tolerated. The authors concluded that memantine might be a potential adjunctive treatment strategy for individuals with ASD.[29] In an earlier open-label add-on therapy study involving memantine, which spanned across a 21-month period with individuals with autism and ASD, participants showed significant improvements in their language functioning, social, and – to a lesser degree – self-stimulatory behaviors.[112]

Acamprosate, a GABA type A agonist and excitatory glutamate antagonist, has also been studied in a recent open-label study. Erickson et al posited that it brought about significant improvements in social withdrawal, hyperactivity, Social Responsiveness Scale, and Clinical Global Impression–Severity scale scores.[113]

The literature, both in the animal and human studies, has suggested that glutamate abnormalities are present in animal models with stereotypies and in clinical populations with ASD. Questions remain unanswered for the specific etiologies resulting in abnormal glutamate levels, which can range from dietary origin to glutamate receptor/transporter problems. However, with this improved understanding of the possible etiology underlying this disorder, pharmacological strategies targeting the glutamate receptors now show promise in ASD, particularly for the core symptoms of stereotypical and social behaviors.

Oxytocin

Recent research has suggested that the neuropeptide oxytocin may play a role in the etiology of ASD. Oxytocin is synthesized in the magnocellular neurons in the paraventricular nucleus and the supraoptic nucleus of the hypothalamus. It is released into the bloodstream by way of the axon terminals in the posterior pituitary. It is released both peripherally (where it is involved in milk letdown and the facilitation of uterine contractions) and centrally, where it acts as a neuromodulator along with arginine vasopressin. Oxytocin (and arginine vasopressin) may play a neuromodulatory role in affiliative and sexual behaviors, separation distress, social memory and recognition, stress response, and the regulation of feeding and grooming. It has been suggested that oxytocin abnormalities may exist in ASD.[114]

Early studies investigated the effects of oxytocin infusion. Findings suggested that oxytocin infusions reduced repetitive behaviors and improved affective speech comprehension from pre- to postinfusion.[115,116] Recent studies have focused on investigating social behaviors in ASD with intranasal oxytocin. In a study that investigated the behavioral effects of oxytocin in 13 subjects with ASD, findings suggested that after an oxytocin infusion, subjects exhibited stronger interactions and increased eye gaze.[117] In another single-armed, open-label study in which oxytocin was administered intranasally to eight male youths with ASD, six of the eight participants showed improved scores on the communication and social interaction domains of the Autism Diagnostic Observation Schedule–Generic (ADOS–G). No side effects were noted.[118]

Several small randomized trials have also been done. In a double-blind, randomized, placebo-controlled crossover trial, an oxytocin nasal spray or placebo was administered to 16 male youths with ASD.[119] In comparison with the placebo, the oxytocin administration improved performance on the Reading the Mind in the Eyes Task.[119] Another pilot, randomized, double-blind, placebo-controlled, parallel design trial was conducted whereby intranasal oxytocin was compared to placebo in 19 adults with ASD.[120] Results also suggested improvements after 6 weeks in measures of social cognition. Additionally, oxytocin was reported to be well-tolerated.[120] Finally, in another trial, intranasal oxytocin was administered to 14 individuals with ASD and 14 neurotypical control participants. They then performed a face-matching and a house-matching task during functional

magnetic resonance imaging. The study was tested in a randomized, placebo-controlled, within subject, crossover design. After oxytocin, right amygdala activity to facial stimuli increased in the ASD group, relative to the control group.[121]

Oxytocin shows promise as a drug targeting the core social and communication deficits in ASD. Further studies with larger sample sizes would be needed to ascertain the efficacy of oxytocin.

Conclusion

The current clinical practice in psychiatry focuses on the use of medications in ASD by targeting specific associated symptoms, not unlike that in the management of other mental health conditions. There are well-established and licensed antipsychotic medications for the treatment of specific symptoms associated with ASD. For example, risperidone and aripiprazole target the management of symptoms, such as irritability and hyperactivity. Findings from trials for other medications have been less consistent. For example, antidepressants and mood stabilizers have been reported to be associated with tolerability issues that need to be balanced against possible benefits. The use of atomoxetine and stimulants remains positive for targeted symptoms, although the ASD population is potentially more vulnerable to adverse events. These medications, coupled with a good clinical understanding of the patient's strengths and difficulties, as well as functional analysis of behavior combined with psychological strategies, may be helpful for some persons with ASD. While the associated symptoms in ASD may be ameliorated, many of these symptoms are manifestations that stem from the core social communication difficulties and repetitive, restricted behaviors in this population. For instance, anxiety in ASD may result from difficulties in peer interactions or problems adjusting to changes in the environment. This intrinsically limits the benefits from traditional pharmacology as the core deficits in ASD are not directly addressed.

Recent research in ASD has moved toward investigating the etiological factors contributing to this complex spectrum of disorders. There is now a growing body of research on genetics, epigenetics, neurological abnormalities, neurotransmitters, hormonal, immunological, prenatal, and environmental factors in ASD. For instance, some studies have investigated the association between immunological factors, such as human leukocyte antigen alleles and ASD.[122,123] Calcium channel membrane proteins, such as the synaptosomal-associated protein of 25 KD (SNAP 25) and the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) protein have also been implicated and findings suggest that polymorphisms of the *SNAP25* gene may be linked to symptomatology in ASD.[124,125] This move toward understanding the basis of ASD will allow a better conceptualization of the disorder from a biological perspective and allow more accurate definition and diagnosis. From a clinical perspective, this will also serve a pivotal role in the clinical approach to managing ASD. Pharmacologically, this will allow the development of medications targeting the biological basis of ASD, hence being more specific and potentially improving the core deficits of this condition. Much of the research in this direction is currently laboratory based. However, there is potential for this work to extend to clinical applicability. Work in glutamate and oxytocin has moved from genetic, epigenetic, and neuronal studies to animal models and, currently, to clinical trials. While findings are preliminary, there are indications that there could be potential benefits in the social communication and repetitive behavioral difficulties with these medications. This calls for collaborative bench to bedside research between scientists and clinicians with a view to breaking new ground in the development of new drugs in the management of ASD.

Disclosure

The authors report no conflicts of interest in this work.

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REVIEW

Unmet needs in the management of schizophrenia

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Abstract: Studies on unmet needs during the last decades have played a significant role in the development and dissemination of evidence-based community practices for persistent schizophrenia and other severe mental disorders. This review has thoroughly considered several blocks of unmet needs, which are frequently related to schizophrenic disorders. Those related to health have been the first block to be considered, in which authors have examined the frequent complications and comorbidities found in schizophrenia, such as substance abuse and dual diagnosis. A second block has been devoted to psychosocial and economic needs, especially within the field of recovery of the persistently mentally ill. Within this block, the effects of the current economic difficulties shown in recent literature have been considered as well. Because no patient is static, a third block has reviewed evolving needs according to the clinical staging model. The fourth block has been dedicated to integrated evidence-based interventions to improve the quality of life of persons with schizophrenia. Consideration of community care for those reluctant to maintain contact with mental health services has constituted the fifth block. Finally, authors have aggregated their own reflections regarding future trends. The number of psychosocial unmet needs is extensive. Vast research efforts will be needed to find appropriate ways to meet them, particularly regarding so-called existential needs, but many needs could be met only by applying existing evidence-based interventions. Reinforcing research on the implementation strategies and capacity building of professionals working in community settings might address this problem. The final aim should be based on the collaborative model of care, which rests on the performance of a case manager responsible for monitoring patient progress, providing assertive follow-up, teaching self-help strategies, and facilitating communication among the patient, family doctor, mental health specialist, and other specialists.

Keywords: schizophrenia, needs, unmet needs, severe mental disorders

Introduction

Since the middle of the last century, three successive approaches can be distinguished in the management of schizophrenia. In the 1960s, management was mainly focused on psychopathology, with little attention paid to contextual factors. Psychoanalysis, family therapy, rehabilitation, and the recently discovered neuroleptics were applied with more or less emphasis, depending on the theoretical affiliations of the clinicians. The needs of the patients and the methods of satisfying them were defined by the medical staff, and as a consequence, they were mainly of a clinical nature.

After deinstitutionalization, patients were faced with the difficulties of living in the community, and their psychiatric management had to take these difficulties into account. As mental health services increased in extension and diversity, management

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http://dx.doi.org/10.2147/NDT.S41063

became more service-oriented. Facilitating access to housing, occupation, company, and social relationships was included in the management of schizophrenia, together with the previously identified clinical aspects.

In the last decades, the rising awareness of human rights and democratic sensibility in society at large has contributed to the empowerment of users of mental health services. Patients and carers both started to get involved in the identification of their individual needs. This resulted in the recognition of needs linked to human rights, such as the need for freedom and respect, and the so-called existential needs, such as the need for spirituality and the need to have a meaningful life.

Further refinement of the management of schizophrenia has been stimulated and supported by the development of instruments for the assessment of needs and the elaboration and diffusion of clinical practice guidelines (CPGs).

Management has become more specific under the influence of instruments developed for describing and quantifying psychopathological symptoms and signs, particularly in clinical research, such as questionnaires, clinical rating scales, and diagnostic interviews. The routine use of these measures is thought to improve decision-making and patient care.[1] Recently, there has been growing interest in including patients' psychosocial performance and quality of life as essential parts of the aims for treatment, with a subsequent emergence of tools developed to measure them.

With the advent of community psychiatry, new tools to assess patients' psychosocial needs were developed. The Camberwell Assessment of Need is a good example of a tool developed to comprehensively evaluate several aspects of an individual's life and mental well-being. The views of staff members and service users are registered separately, allowing differences of opinion to be identified and a management plan to be negotiated.[2]

The prominence gained by users and their relatives in health care has led to their participation in the elaboration of new instruments, such as the Maristan Scale of Needs.[3] This instrument is based on qualitative data obtained from users, carers, and professionals across several cultures and contains four factors: health needs, work and leisure needs, existential needs, and needs for support in daily life.[3,4]

In addition to their contribution to refining management and supporting decision-making, these instruments have helped to detect, define, and measure unmet needs and to identify new needs. Information about unmet needs may be obtained by directly asking the patient about them in the course of routine interviews; by making inferences from data, as well as from epidemiological surveys; or by using established needs assessment instruments.[5]

From a public health perspective, the unmet needs of persons with schizophrenia who have not made contact with health services are also a major problem. The treatment gap (TG) for schizophrenia across the world, including other nonaffective psychoses, has been estimated at 32.2% by the World Health Organization.[6]

CPGs gather recommendations, based on research evidence, on how to manage schizophrenia. More than 20 CPGs from 18 countries have been published and are in use at the present time.[7] Despite the fact that CPGs are widely known and contain viable and effective recommendations, actual implementation is often suboptimal. Discordance in CPG recommendations regarding psychosocial interventions[8] may not help reduce observed practice variations in this area, but even in the area of psychopharmacology, evidence suggests that the management of schizophrenia is often poor.[9] Inadequate implementation of CPGs may be caused by scarce resources, poor management of the available resources, and the effects of stigma. Multiple strategies have been proposed to improve CPG implementation.[10]

In summary, the management of schizophrenia at present is not supported by a finished and coherent body of scientific evidence but has, rather, developed during the last 50 years as a complex process of interactions among research, professional practice, service provision, user's experience, and mental health advocacy, and it is still evolving.

Unmet health care needs: complications and comorbidities of schizophrenia

Despite considerable advances in the process of care, schizophrenia and its related mental disorders are quite often associated with negative health outcomes. Plausible determinants include adverse effects of medication, drug abuse, smoking, inactivity, and disorganized patterns of nutrition and hygiene, which may facilitate the occurrence of serious comorbid medical problems such as obesity, metabolic syndrome, diabetes, and cardiovascular disorders, as well as chronic infective disorders. Substance abuse is the most common comorbidity among patients with schizophrenia and has a strong effect on the clinical picture (psychopathology), diagnosis, course of treatment, and prognosis.

Because of specific clinical characteristics (eg, delusions, negative symptoms, neurocognitive dysfunction, and disorganization), schizophrenia may impair the patient's capacity to identify symptoms of medical illness, report

them to health professionals, and engage in treatment, in addition to complying with regular medical appointments plus prescribed medication.

Studies on the relationship between psychopathological symptoms in schizophrenia and quality of life have shown that negative symptoms and general psychopathology are the best predictors of quality of life in these patients.[11] In contrast, the severity of negative symptoms and cognitive deficits are the best predictors of the objective dimension of quality of life.[12] In addition, a higher severity of symptoms is related with a lower quality of life.[13]

Somatic conditions

The literature shows that there is a significant association between schizophrenia and several somatic disorders such as nutritional/metabolic disorders, cardiovascular conditions, and sexual dysfunctions, among others. Obesity, diabetes, and smoking are two times more frequently seen among patients with Severe Mental Disorder (SMD) than in the general population.[14] These conditions may compromise medication compliance and the quality of life of patients with schizophrenia. Furthermore, life expectancy in schizophrenia is reduced, with an excess mortality that is two times higher than that in the general population,[15,16] with cardiovascular diseases responsible for 50% of the excess mortality associated with schizophrenia diagnosis.[17–22]

Despite the contribution of several factors, the most important determinants of the poor somatic health of this population seem to be lifestyle-modifiable risk factors (smoking, alcohol, drugs, and lack of exercise), adverse effects of prescribed psychotropic medication, and poor access to good-quality mental health services. In fact, although psychiatrists are conscious of potential somatic problems in persons with schizophrenia, physical health assessment and management have been reported frequently as being scarce.[23] This poor recognition of somatic conditions might be a result of reduced physical assessment skills, particularly after a long time of exclusive psychiatric practice.

Metabolic and nutritional problems are among the most reported findings not only in schizophrenia but also in other SMD. In schizophrenia, an increased likelihood risk for overweight, obesity, and abdominal obesity is present even in recently diagnosed and nonmedicated patients.[24] Psychotropic medication is strongly associated with sexual dysfunctions[25] and obesity,[26] particularly in patients with significant negative symptoms, reduced social interaction, and disorganized behavior. Both conditions limit patients' everyday interpersonal relationships and frequently become their reason to reject medication. Although most antipsychotics may cause overweight, the risk seems greater for clozapine and olanzapine and smaller for aripiprazole and ziprasidone, with quetiapine and risperidone showing an intermediate risk profile.[27,28] Mood stabilizers, such as lithium and valproate, and several antidepressants, particularly the tricyclic antidepressants, are also associated with a significant risk for obesity in schizophrenic patients.[29]

Patients with schizophrenia present with an excessive risk for metabolic syndrome (MS).[30,31] Obesity and insulin resistance are core components of MS, together with hypertension, elevated triglycerides, and established determinants of diabetes. MS is strongly associated with increased mortality because of cardiovascular risk and might be present in almost half of the psychotic patients even 20 years after their first psychotic episode.[32] Patients prescribed with second-generation antipsychotics show a higher incidence rate of MS than patients treated with first-generation antipsychotics.[33] Despite this evidence, metabolic screening and monitoring are still limited, even in developed countries with effective health systems.[34]

Regarding type 2 diabetes, the prevalence of this illness in patients with schizophrenia is five times higher compared with in the general population, with a significant association with clozapine and olanzapine. Moreover, the TG of diabetes among schizophrenic patients remains quite high, reaching nontreatment rates around 40% in large-scale multicentric studies.[35,36] The elevated prevalence of these metabolic problems may explain why the death rate from cardiovascular disorders in schizophrenic patients has not declined in recent years in developed countries, as it has in the general population, and stands as the first cause of mortality among patients with SMD.[18,37] Patients with schizophrenia and other SMD are at greater risk of coronary heart diseases,[19] stroke,[38] ventricular arrhythmias,[39] and sudden death.[40] Given that the excess of cardiovascular mortality is, at least partially, a result of modifiable risk factors (lack of exercise, obesity, smoking), there is a need to improve the access of schizophrenic patients to primary care facilities, where these issues can be evaluated and monitored first-hand.

In addition to metabolic and cardiovascular diseases, particular attention should also be given to other conditions frequently associated with poor physical outcomes in schizophrenia. For instance, in places where institutionalization remains the principal model of care, infections such as pneumonia and tuberculosis are still more prevalent in the institutionalized population than in noninstitutionalized populations.[41,42] Heavy smoking, a strong risk factor for

respiratory disorders, is much more common among psychiatric patients diagnosed with schizophrenia, particularly in long-term institutionalized patients, than in the general population (80% versus 20% in the adult population).[43] Restoration of nicotine function, amelioration of unwanted dopamine blockade adverse effects, and improvement of cognitive and negative symptoms have been reported as possible causes for this finding, according to neurobiological research findings.[43]

In addition, considerable risk for the occurrence of diseases caused by viral infections, such as HIV (estimated to be 4%–23%),[26] hepatitis B, and hepatitis C, which is often related to intravenous drug abuse and unprotected sexual activity, has been systematically reported in schizophrenic patients.[44]

Although schizophrenia has been associated in several well-conducted studies with a decreased risk for cancer even after controlling for smoking, there are yet some conflicting results, and the subject is not closed.[45] Possible sources of bias are the decreased access of psychotic patients to general medical services, the lower rate of autopsies among those patients, and the poor quality of some mental health case registers.[46] More important from an organizational perspective, a large-scale study conducted in Australia showed that despite the lower incidence of neoplasm in schizophrenia patients, mortality resulting from cancer was increased (39% higher in men and 24% higher in women; range, 17%–32%) when compared with the general population, suggesting once again an unmet need in the access of those patients to medical services.[47]

Hyperprolactinemia, a common adverse effect of first-generation antipsychotics, has also been associated with breast cancer, osteoporosis, and hypogonadism, but the results are contradictory.[48]

Substance abuse and dual diagnosis

According to recent data, only 12.4% of American adults with dual diagnosis receive both mental health and substance abuse treatment.[49] Comorbidity may be a result of several factors, probably in association. Mental disorders may predispose to the onset of substance use disorders in situations such as disinhibition, mood swings, overwhelming anxiety, and the adverse effects of medication. In contrast, substance use disorders may lead to the onset and maintenance of mental disorders through biological mechanisms such as heavy cannabis use during adolescence or comorbid panic and cocaine abuse resulting from brain kindling. Finally, common genetic and environmental causes should not be disregarded, as they may share similar physiopathological processes leading to an increased lifetime risk for comorbidity.

Epidemiological estimates of dual diagnosis may change with the definition criteria, the ability of mental health professionals to detect the problem, and the tools used to measure the disorders. Taking into account these methodological limitations, prevalence rates are still very substantial.

In the National Comorbidity Survey, 51.4% of respondents with a lifetime diagnosis of substance abuse disorder (including alcohol and drugs) also met criteria for at least another lifetime mental health disorder, with an odds ratio of 2.4.[50] Other studies conducted in different places and settings also show high prevalence rates of comorbidity, ranging between 37% and 53%, both in community surveys and clinical samples.[51] Conversely, up to 66% of patients with schizophrenia meet criteria for at least a single substance-related disorder in their lifetime.[51]

There is growing evidence that patients with a dual diagnosis do not respond well to conventional psychiatric treatment, creating demand for a new approach from a different perspective.[52] In fact, particular attention has to be given to the characteristically greater clinical severity, the greater exposure to environmental risk factors, the potential abuse of currently used pharmacological agents, and the lack of specific training of mental health professionals in dealing with this population. The shortage of trained clinicians as well as the widespread scarcity of specialized facilities offering integrated programs, even in developed countries, is a strong determinant of the high level of unmet needs for care in this area.[53]

Other psychiatric comorbidities

Psychiatric comorbidities are much more common among patients with schizophrenia than what would be expected by chance alone.[54] Anxiety and depressive symptoms are seen quite frequently during the course of illness, with an estimated prevalence of 15% for panic disorder, 29% for posttraumatic stress disorder, and 23% for obsessive-compulsive disorder. Surveys estimated that depression occurs in 50% of patients with schizophrenia, both during and after the emergence of florid psychotic symptoms.[55] In addition, depression reduces quality of life in schizophrenic patients.[56,57]

A recent systematic review of suicide in schizophrenia[58] reported that lifetime risk of suicide was approximately 5%. Risk factors included young age, being male, being educated, prior suicide attempts, depressive symptoms, active hallucinations and delusions, substance abuse, and the presence of insight. According to this review, delivery of

effective treatment was the only reliable protective factor for suicide.

As we have shown, there is scientific evidence that patients with schizophrenia require comprehensive care focused on both their mental and physical needs.[22] However, these patients are not regularly examined to assess their physical condition and the possible organic effects of pharmacological treatments. It is only recently that specific assessment protocols have been established for the follow-up of obesity, sedentary lifestyle, and life habits in these patients. In addition, patients with schizophrenia have more difficulties getting access to primary care[59] and are less likely treated for physical problems.[60] In the absence of scientific evidence for specific interventions, the use of CPGs is recommended to mitigate cardiovascular risk in patients with schizophrenia.[61]

Unmet psychosocial and economic needs

Patients with schizophrenia usually present with difficulties in diverse areas of daily life: they are predominantly unemployed, single, and have a low educational level.[62–64] They have also difficulties with housing, as the Team Assessment Psychiatric Services (TAPS) project described[65] and current literature emphasizes,[66] and their income depends on community aids.[67] A high proportion of patients with schizophrenia have little or no social contact or friends, present with a high risk of isolation, and have difficulties getting involved in leisure activities.[67]

In general, unmet needs differ depending on the sociocultural environment. Results from the European Psychiatric Services: Inputs Linked to Outcomes and Needs (EPSILON) study comparing users' needs in five European cities showed that needs diverge in different contexts and that more unmet needs were found in big urban areas,[68] where poverty, unemployment, and other social problems are more severe.[69] Psychosocial needs were reported by users as the most unmet and included daily activities, company, and intimate relationships.[70] Similar findings were found in studies with users from Nordic countries, where psychosocial needs were also the most unmet, particularly those related to social relationships,[71] which were also the most related to patients' quality-of-life perception.[72] Social contact is one of the main domains related to quality of life and is the area in which schizophrenia patients claim the most dissatisfaction. Moreover, frequency of contact with relatives or friends has been shown to be a predictor of quality of life.[73] Inversely, stigmatization and social exclusion may negatively affect perceived quality of life in patients with schizophrenia.[74] It has been proven that patients presenting with a higher quality of life show a better perception of family functioning, which confirms the importance of families as social and emotional support networks and agents in meeting individuals' needs.[75] In a Spanish study, users identified as unmet those needs related to health and social services provision, including psychotic symptoms, house upkeep, food, and information.[76] These results were similar to those presented in a study comparing patients' needs in five European and Latin American countries, where Argentinean patients identified more needs related to health care, probably because of the fragmentation of their health system and their dependence on psychiatric hospitals.[3] In India, a study found that two-thirds of patients' needs were unmet, the most important of which were psychotic symptoms, psychological stress, information, and money.[77]

The organization and provision of care in health systems, together with life conditions in the cities, undoubtedly influence needs satisfaction. When these systems are less wealthy, instrumental and economic aspects become more important; when these needs are satisfied, patients give more weight to social relationships.

Unmet needs can be classified in different levels (eg, community or health services) and from different perspectives (eg, users, families, and health teams). Mojtabai and colleages[78] pointed out that according to epidemiological studies in the United States, at least 40% of patients with schizophrenia continue living in the community without any type of treatment for long periods of time, even if they present with significant symptoms. The main barrier for access to services is stigma associated with mental illness. Thus, negative perceptions about mental illness in the users are related to a higher number of unmet needs and to negative attitudes toward medication.[79] In contrast, there is another group of patients that uses health services but presents with scarce adherence to treatment. In both groups, unmet needs are estimated from the comparison between recommended treatments and service use patterns.[78]

Along these lines, it has been shown that users present with different needs, depending on the type of intervention they are receiving. Cleary and colleagues[80] found that patients with SMD, both in inpatient and community settings, shared the same unmet needs (daily activities, company, and intimate relationships) but that these needs were greater among institutionalized patients. In contrast, it has been shown that patients using long-term services require promotion of independence, stability in housing, stability in social networks, consistency of care, and addressing the theme of loss.[81] Apparently, the

unmet needs of users attending community and rehabilitation services tend to increase and change over time, with psychosocial needs perceived as the most important.[82] In a study comparing the needs of users under rehabilitation programs in two points in time, more unmet housing and money needs were found in the present compared with in data from 1998.[83] These results lead to the hypothesis that needs are also sensitive to sociocultural changes, which could limit its use in services comparing assessment.[84]

Most studies agree that users, relatives, and health staff differ on their perceived unmet needs.[85,86] A recent study found that health personnel reported a greater number of unmet needs than users.[87] For the latter, unmet needs are mainly focused in the areas of social, personal, and intimate relationships.

In contrast, unmet needs also depend on the vital cycle stage and, thus, on the illness stage the patients are in. In older adults, most unmet needs are focused in the psychosocial and general health care areas,[88] and the psychosocial and social areas are less covered than the environmental and physical areas.[89] However, studies on first-episode psychosis are scarce. In one of these few studies, young people reported that 20% of their needs were unmet.[90]

These data are alarming, as most social impairment in schizophrenia occurs at the beginning of the illness, between the second and the fifth year after onset.[91] This is why treatment of first episodes emphasizes not only symptoms reduction but also prevention of social decline. In the only longitudinal study published so far on the needs of first-episode schizophrenia patients, results showed that daily activities, psychotic symptoms, psychological stress, and social integration were most frequently reported as unmet needs. In the follow-up, second-generation medication showed no effect on the course of unmet needs.[92] Antipsychotic treatment alone was not sufficient to account for the psychosocial needs of patients. In spite of that, interventions are still focused on symptoms management, instead of on rehabilitation or on improving social and occupational functioning.[78] In contrast, unmet needs have been associated with risk behaviors such as aggression[93] and can predict suicide when unmet need is related to interpersonal contact.[94]

It is important to bear in mind that, conversely, quality of life is also influenced by sociodemographic factors such as unemployment,[75,95] sex, or age.[73] It also has been found that male and older patients present with a poorer quality of life. In addition, the gap in unemployment rates between individuals with and those without mental health problems is significantly widened by financial crisis.[96] Recent evidence supports that mental health recovery services should include programs that address employment issues.[97]

The clinical staging model

In the last 15 years, a new diagnostic approach has been developed in an attempt to overcome the limitations of the current diagnostic system (lack of validity and therapeutic utility): the clinical staging model.[98] According to this model, studying the course, extension, and pattern of illness over time provides a more useful diagnostic system for both clinical practice and research. This model is based on the idea of providing the earliest possible effective intervention that could prevent progression to more advanced stages, or even promote regression to an earlier stage, including total remission.[98] The identification of early clinical symptoms is the focus of this model, which makes it especially useful for adolescents and young adults – those at the age when onset of psychotic disorders usually occurs. The rationale for this focus on early detection and intervention is the robust association between longer duration of untreated psychosis and poorer response to treatment both on a short- and long-term basis.[99,100]

According to the clinical staging model, psychotic disorders evolve through three initial stages: the ultra-high risk (UHR) stage, the first-episode psychosis (FEP) stage, and the critical period of early psychosis.

Criteria for the identification of individuals at high risk (UHR) include attenuated positive psychotic symptoms, brief self-limited psychotic symptoms, and family history of psychotic disorder.[98] Using these criteria, around 40% of individuals identified as UHR presented with FEP within a 1-year follow-up, even after receiving needs-based psychosocial interventions.[98,101–105] Studies on different intervention approaches in the UHR stage of psychosis have come to the conclusion that first-line treatments in UHR patients must be mild, including psychosocial interventions such as cognitive-behavioral therapy (CBT) or supportive therapy, or supplementation with eicosapentaenoic acid. If necessary, pharmacological approaches could also be employed, with aripiprazole as the best candidate.[98]

Once a full psychotic episode is detected, the patient enters the FEP stage. In this stage, the main objective is to obtain the patient's engagement in pharmacological and psychosocial treatments. Interventions in this stage are broadly described in the International Clinical Practice Guidelines for Early Psychosis,[106] published in 2005, and were supported by the European First Episode Schizophrenia Trial (EUFEST) study[107], favoring second-generation antipsychotics as

first-line therapy in FEP, given their better tolerability. The inability of medications to produce significant improvements in patients' functioning has produced an increased interest in psychosocial interventions such as the need to enhance social recovery,[108] especially in the educational and vocational field.[109,110] In addition, cognitive remediation is one of the focuses in this stage.[111,112] In summary, in this stage, both effective psychosocial intervention and well-managed medication are fundamental to avoiding progression of the illness.

The critical period in early psychosis is defined as the first 2–5 years after the diagnosis of a psychotic disorder. This is a very important stage, as it coincides with major developmental challenges such as forming a stable identity, peer network, vocational training, and intimate relationships.[98] Treatment in this stage is aimed at minimizing the risk for relapse and the disability associated with the disorder, as well as maximizing social and functional recovery. Moreover, interventions should also be focused on maximizing the chances of treatment engagement, continuity of care, appropriate lifestyle, family support, and vocational recovery and progress. This can be achieved through patients' engagement in combined pharmacological and psychosocial interventions. However, here we find a huge TG between what is needed and what is provided, even in most developed countries[113,114] (see section on Community Care for those reluctant to maintain contact with mental health service).

Nowadays, mental health services, particularly those oriented toward rehabilitation, promote a recovery view of service. Recovery is an individual process implicating the development of a new meaning and purpose in life beyond the psychiatric illness.[115] Needs assessment permits going further than recovery from an individual point of view, as it shows where intervention is more important not only from the patient's but also from the social environment's point of view.[87] As a consequence, needs assessment can be considered an articulating tool between the patient and the social environment beyond the illness itself.

Integrated evidence-based interventions to improve the quality of life of persons with schizophrenia

Quality of life has been considered as a unified concept to assess the effect of illness on daily life of people with schizophrenia.[116] The main dimensions to assess this construct include psychopathological state, physical health, sociodemographic factors, level of functioning for daily life activities, and social relationships, understood as interpersonal contacts and involvement in social and leisure activities.[117–120] There is a general accord in considering that quality of life should reflect a person's well-being, both at the objective and subjective levels, and that it refers to general satisfaction with life. The literature on this issue has shown that patients with schizophrenia present with a lower quality of life compared with healthy people in the community.[116]

Although the treatment of patients with schizophrenia has been traditionally focused on symptoms, given that they are associated with hospitalization episodes, it is nowadays considered that this treatment must be more comprehensive and must allow integration of patients into their community. This is why quality of life has been considered to be a main target in the treatment of these patients.[95]

Although it is obvious that drugs alone are not enough for facing schizophrenia, most schizophrenic patients will need to be treated with antipsychotics. The sooner the patient is treated with antipsychotics after the onset of the disease, the better overall outcome. It is a severe risk for the patient if this worldwide-accepted axiom is forgotten and antipsychotics also become an unmet need.

Several evidence-based pharmacological and psychosocial interventions to alleviate symptoms and improve functioning and quality of life of persons with schizophrenia are also available. Some of these interventions have been put together in packs of integrated care, such as the Optimal Treatment Project[121] and the Patient Outcomes Research Team (PORT) report,[122] and their feasibility and cost-effectiveness have been proved in naturalistic studies.

A recent systematic review and meta-analysis comparing antipsychotic drugs with placebo on relapse prevention in schizophrenia concluded that sustained antipsychotic treatment of patients diagnosed with schizophrenia lowers their risk of relapse, especially when depot preparations were used and independent of whether the antipsychotic belonged to the classic or the new generation of drugs. Authors recommend further studies focused on outcomes of social participation and related to long-term mobility and mortality rates induced by these treatments.[123]

Another extensive (data for 43,049 participants) and recent meta-analysis shows a comparison of the efficacy and tolerability of 15 antipsychotic molecules. According to the results, all drugs were significantly more effective than placebo, and the different molecules differ clearly in adverse effects and prove "small but robust" differences regarding their efficacy. Moreover, the authors question the accepted hierarchy of first-generation and second-generation antipsychotics, finally recommending the use of the drug best adapted to the needs of the individual patients.[124] With regard

to this issue, in routine clinical practice it is advisable to follow the findings and recommendations of the thoroughly detailed PORT study on schizophrenia.[122]

Falloon and colleagues conducted a multisite, worldwide (>80 centers), naturalistic study that should also be commented on. The authors designed an "Optimal Treatment" package including only evidence-based strategies, with the main components being minimally effective antipsychotic drug strategies targeted to change symptom profiles, education of patients and informal carers in stress management strategies, assertive case management, goal-oriented social and occupational skills training, and specific pharmacological and/or psychological strategies for residual or emerging symptoms. The authors used a nonrandomized sample and did not apply the common exclusion criteria (comorbidity, dual diagnosis, etc), so the sample represented only typical clinical cases. According to their results, the combination of pharmacological and psychosocial strategies that had previously proven efficacious in controlled trials can be applied in routine practice without additional resources. The authors maintain that integrated optimal pharmacotherapy and psychosocial treatment programs may play a major role in expediting recovery from psychotic disorders and also are cost-effective.[121]

A very recent contribution by Mueser and colleagues offers additional evidence and claims for the clinical integration of empirically supported psychosocial interventions for schizophrenia.[125]

Respect for human rights of the mentally ill

Since the early 1990s, most international bodies have shown an increasing interest in the dignity of, the empowerment of, and respect for the mentally ill.[126,127] Undoubtedly, this is a result of the "lobby-like" action of growing user movements, but certainly it is also a result of the new, predominant fieldwork of therapists: the community. Users and professionals were becoming aware that they also have to face new challenges, including stigma and social needs, among many others.

Also in the 1990s, the World Psychiatric Association started an ambitious Global Program to Reduce Stigma, known as Open the Doors.[128] However, the results did not support the utility of an antistigma campaign with a broad approach but, rather, suggested a more specific focus, such as perceived dangerousness.[129] The profound association in people's imagination between dangerousness and mental disorder, especially schizophrenia, constitutes a strong reality reinforced by media, and the fight against that connection should not be eliminated from any plan for mental health action.

One of the most common risks of a person suffering from schizophrenia under community care is being admitted to a hospital because of his or her mental conditions. The mere fact of hospitalization is a risk in itself because of the added stigma, plus the frequent suffering of lowering self-esteem and loss of dignity perception when coerced into involuntary treatment. Moreover, mostly if admitted compulsory, patients may also suffer other means of coercion to restrain their movements, such as mechanical constraint, isolation, or administration of nontherapeutic aimed drugs.

All this was extensively considered in the European Evaluation of Coercion in Psychiatry and Harmonization of Best Clinical Practice (EUNOMIA) study, supported by the European Commission in 12 countries.[130–132] For the purposes of this review, the EUNOMIA findings can be summarized as follows:

1. There is a great heterogeneity on legislation across Europe regarding required conditions and procedures for compulsory admission.[131]
2. In most countries, the conditions and procedures for applying other coercive means were not regulated.[131]
3. The mere voluntary hospitalization is not a harmless decision to the patient. Patients who feel coerced, even those who have been voluntarily admitted, may have a poorer prognosis than those involuntary admitted legally.[133]
4. Future studies should identify the factors in legislation and clinical practice, including important staff–patient interactions, that could lead to a more constructive cooperation of all parties involved.[132]

We could add that when some users were asked in focus groups (not published), none of the coercive measures were naive to the patients, and in some cases patients felt them as an attack on their dignity. This statement certainly needs more research, using an appropriate qualitative method if possible.

Restoring users' dignity and self-esteem through their progressive empowerment and autonomy should be part of any recovery program. Quite a few of the most recent documents of the international bodies and multinational agencies support this and offer similar recommendations toward the same aim.[130,134,135] However, the need for a better coordination of the different strategies and plans of action launched by

these international institutions to guarantee the commitment of their member countries is noticeable.

Community care for those reluctant to maintain contact with mental health service

For a long time it has been known that there are patients who show unmet needs of service contact or unmet needs of psychosocial contact and of pharmacological treatment. A worldwide figure of unmet needs or TG for SMD was 32%, according to a World Health Organization report.[6] In 20014, another World Health Organization European study[136] showed that the TG of SMD living in the community ranged between 35.5% and 50.3%, including in the most developed countries.

Lack of insight, past experiences, and prejudices against health services, among other reasons, make this group of people reluctant to maintain therapeutic links. They live in the community, and without adequate treatment, they are at risk of progressive health deterioration, forced reinstitutionalization, or even imprisonment.[137,138]

The first of the two previously mentioned World Health Organization reports[6] proposed ten recommendations to address the TG:

1. Mental health treatment should be accessible in primary care.
2. Psychotropic drugs need to be readily available.
3. Care should be shifted away from institutions and toward community facilities.
4. The public should be educated about mental health.
5. Families, communities, and consumers should be involved in advocacy, policy-making, and forming self-help groups.
6. National mental health programs should be established.
7. The training of mental health professionals should be increased and improved.
8. Links with other governmental and nongovernmental institutions should be increased.
9. Mental health systems should be monitored, using quality indicators.
10. More support should be provided for research.

More recently, a systematic World Psychiatric Association survey of leaders of psychiatry was completed in almost 60 countries, examining strategies to reduce the TG. The authors concluded that "scaling up of mental health services can only be achieved effectively if three elements are in place: task shifting to non-specialist providers; an increase in the specialist mental health resources to provide effective and sustained supervision and support; and a decentralization of those specialized mental health resources."[139]

Mental health services policy makers have been concerned about TG over the last decades, and many attempts have been made to solve it. Case management, intensive case management, assertive community treatment, and assertive outreach are or have been the most common names used to refer to successive models of community care specifically oriented to satisfy the unmet needs of the SMD.

It has been long known that assertive outreach and intensive case management can reduce hospitalizations of patients who are frequent users of inpatient care and can reduce overall mental health care costs. In addition, greater fidelity to the models produced better outcomes.[140,141] This has also been validated in rural areas.[142]

SMD is very frequently found in the excluded homeless population, making it more difficult to engage them in services care. It is then that assertive community treatment offers significant advantages in reducing homelessness and symptom severity in homeless people with SMD.[143] The best outcomes for housing stability were found for programs that combined housing and support.[144]

These models of intensive care outreach services can have significant benefits in terms of patient outcomes and service use. Moreover, the implications of specific nursing programs provide a useful framework for evaluating the effect of these services.[145]

A recent Cochrane review found that intensive models of community care were more effective for several relevant outcomes of people with SMD. These not only reduced hospitalization and increased adherence to care but also improved social functioning, although the effect on psychopathology was not so clear.[146]

The effectiveness comparison of numerous attempts of available community models would be beyond the scope of the present revision. In summary, though, we could say there is a general accord on four basic criteria: the outreach team should be mobile instead of based at a mental health center; the team should have its own, full responsibility for care of a given bunch of clients; the caseload/staff member ratio should remain low; and the care at the client home should be part of the team routine.

Very recently, a Cochrane Systematic Review considered a new movement aimed at increasing the adherence of those patients with SMD who are reluctant to seek care. The review compared past or present users of mental health centers that

were providing care versus professionals enrolled in case management. There were no significant differences between the two groups in clinical psychopathology, satisfaction, adherence to care, or withdrawing from the study, among other variables. Those receiving care from past or present users of mental health services used crisis and emergency services slightly less frequently than those receiving care from professional staff. Regarding care procedure, it was found that past or present users spent more face-to-face time with patients. The author invites others to further research this matter, reinforcing the methodological approach and changing the location in diverse settings, including low- and middle-income countries.[147]

Reflections regarding future trends

The number of psychosocial unmet needs is extensive. Vast research efforts will be needed to find appropriate ways to meet them, particularly regarding the so-called existential needs, but many could be met only by applying existing evidence-based interventions. Despite the general awareness of protocols, algorithms, and clinical practice guidelines, research findings are slow to reach into the daily management of schizophrenia, and many useful and cost-effective techniques are ignored in practice.[148] Reinforcing research on implementation strategies and the capacity-building of professionals working in community settings might help address this problem.

Regarding unmet health needs, evidence-based organizational techniques for the management of chronic disorders could be applied extensively to severe mental disorders.[149,150] The Collaborative Model of Care may facilitate early detection and therapy of somatic disorders and improve treatment compliance in people with schizophrenia. This model of care rests on the performance of a case manager responsible for monitoring patient progress, providing assertive follow-up, teaching self-help strategies, and facilitating communication between the patient, the family doctor, the mental health specialist, and other specialists.

There are also unmet needs brought about by the psychiatric interventions themselves. Antipsychotic medications, while improving positive symptoms, may cause a variety of adverse effects that seriously interfere with quality of life. Use of low dosages, and even discontinuation of these medications in judiciously selected cases, will help to alleviate this problem as well as improve long-term functioning.[151]

Serious damage to quality of life may also come from some psychosocial interventions. The use of coercive procedures such as compulsory admission, community orders, or simple leverage, whether clinically justified or not, can be extremely detrimental to the quality of life. What is more, authoritarian and stigmatizing attitudes of mental health professionals frequently act as a barrier for the identification of a patient's preferences and needs. The participation of users and relatives in the planning and evaluation of mental health services and the growing collaboration between users, families, and mental health workers are key factors in bringing about the necessary change in these attitudes and behaviors. The incorporation of users in providing formal care within statutory mental health services is another example of this collaboration.[147]

One major advance in approaching the management of schizophrenia comes from conceiving it as a neurodevelopmental disorder that progresses in identifiable stages. Each developmental stage, modulated by sex and the phases of the vital cycle, is associated with different medical and psychosocial needs, and hence requires different and specific interventions.[152,153] In this context, management interests are presently being displaced from cognitive impairment and negative symptoms during the chronic phase to the early stages of development.

Another issue concerns social policy and the availability of community facilities to cover basic social needs. Quality of life is associated with employment, income, and housing stability. Unemployment, poverty, and housing instability are high among people with mental health problems, and even more so in times of economic recession.[96] Social policies designed to cover these basic needs are a must if we want to avoid institutionalization and maintain the quality of life of people with schizophrenia. Along these lines, the preservation of the welfare state is critical. During the last decade, coinciding with the economic crisis and as a consequence of a tide of privatizations driven by neoliberal ideologies, some public health services in Europe are being dismantled. Advocacy for protecting the basic rights of persons with SMD is now more necessary than ever.

Disclosure

The authors report no conflicts of interest in this work.

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REVIEW

New generation multi-modal antidepressants: focus on vortioxetine for major depressive disorder

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Abstract: Vortioxetine is a novel antidepressant with effects on multiple 5-HT receptors and on the serotonin transporter. This paper reviews preclinical and clinical evidence regarding its mechanism of action, its tolerability, and its efficacy in treating major depression. Clinical studies indicate that vortioxetine is effective in the treatment of major depression, though there is no suggestion of superiority over active comparators. There may be a clinically meaningful advantage in terms of tolerability.

Keywords: vortioxetine, major depression, review

Overview of current treatment strategies for major depressive disorder (MDD) and their limitations

MDD is one of the leading causes of disability in both the developed and the developing world. It has consistently been found to be associated with significant reductions in quality of life, impaired work productivity, reduced social functioning, poor physical health, and substantial direct and indirect economic costs. According to the World Health Organization's Global Burden of Disease project,[1] MDD will become the second leading cause of disability worldwide within the next 10 years.

Antidepressants, together with evidence-based psychological therapies such as cognitive behavioral therapy, are important components of current treatment for major depression. Their efficacy is, however, quite limited. Only about 30%–40% achieve a full remission after a single adequate course of antidepressants. A further third have a clinically significant response to antidepressant therapy but have residual symptoms which limit their social functioning and increase their risk of relapse.[2]

Treatment adherence is a further problem.[3] Fewer than half of patients with MDD take their antidepressants consistently and for the full recommended duration. This reflects the delayed onset of action associated with antidepressant use and their considerable side effect burden. Common side effects (which are often prominent in the weeks before any clinical response becomes evident) include weight gain, sexual dysfunction, nausea, headache, and sleep disturbances. There is therefore, a clear need for novel antidepressants with distinct mechanisms of action and improved side effect profiles.

Vortioxetine, an antidepressant produced and co-marketed by Lundbeck and Takeda, was approved by the US Food and Drug Administration under the trade name Brintellix. At the time of writing, vortioxetine remains under consideration by the European licensing authorities. This paper reviews the mechanism of action

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http://dx.doi.org/10.2147/NDT.S39544

of vortioxetine, the evidence regarding its safety and efficacy, and its potential place in the depression treatment armamentarium.

Novel mechanism of action of vortioxetine

Vortioxetine was developed as one of a series of compounds developed from halogenated benzenes and was intended to have combined effects on multiple 5-HT receptors and on the serotonin transporter. It has been shown in recombinant cell lines to combine 5-HT_3 and 5-HT_7 receptor antagonism, 5-HT_{1B} receptor partial agonism, 5-HT_{1A} receptor agonism, and serotonin transporter inhibition.[4]

Review of pharmacology, mode of action, and pharmacokinetics of vortioxetine

Mørk et al[5] assessed the effects of vortioxetine on brain neurotransmitter levels in vivo in freely-moving rat models predictive of antidepressant and anxiolytic-like activity. They confirmed that vortioxetine had multimodal serotonergic actions including partial 5-$HT1_B$ receptor agonism, 5-HT_7 antagonism, 5-HT_3 antagonism, and inhibition of the serotonin transporter.

Bétry et al[6] used electrophysiological and autoradiography studies in male Sprague–Dawley rats to examine the acute and chronic effects of vortioxetine on 5-HT neuronal firing activity and to compare them with the effects of the selective serotonin reuptake inhibitor fluoxetine. Vortioxetine caused a rapid decrease in spontaneous firing of 5-HT neurons in the dorsal raphe nucleus, which (in contrast with the effects of fluoxetine) recovered within 1 day. Subsequent autoradiographic studies indicated that 5-HT neuronal firing was inhibited by vortioxetine at doses that only partially blocked the serotonin transporter. Vortioxetine administered for 3 days desensitized 5-HT_{1A} autoreceptors to the effects of the 5-HT_{1A} agonist flexinoxan. The authors concluded that vortioxetine inhibited 5-HT neuronal activity indirectly by inducing the release of extracellular 5-HT and suggested that 5-HT_3 receptor antagonism was also an important aspect of its mechanism of action.

Pehrson et al[7] examined the effects of acute and subchronic treatment with vortioxetine (compared with escitalopram) on extracellular 5-HT norepinephrine (NE) and dopamine (DA) levels in a rat ventral hippocampus (vHC), medial prefrontal cortex, and nucleus accumbens, as well as its effects on NE and DA neuronal firing in the locus coeruleus and in the ventral tegmental area. 5-HT levels were increased by vortioxetine (most markedly in the vHC) despite quite low 5-HT receptor occupancy. NE and DA levels were also somewhat increased in the vHC and medial prefrontal cortex but not in the nucleus accumbens. The authors concluded that vortioxetine had two main mechanisms of action (5-HT receptor modulation and serotonin transporter inhibition) through which it induced region-dependent increases in the concentration of multiple neurotransmitters.

Single dose human studies show that vortioxetine is extensively metabolized in the liver, and is a substrate for a range of cytochrome P450 (CYP450) isoforms.[8] In vitro studies using human liver cells indicate that vortioxetine has no CYP450 inducing or inhibitory effects.[9,10]

Areberg et al[11] carried out an extensive human pharmacokinetic study. They administered vortioxetine by mouth and intravenously in a total of 97 healthy volunteers aged 18–51 years (median 24). Vortioxetine had an extended absorption phase and medium clearance. The volume of distribution was large, indicating that vortioxetine is lipophilic with high affinity for peripheral tissues. Once a steady state was reached, plasma vortioxetine levels varied little throughout the day. The absolute bioavailability was 75%. Mean elimination half-life following oral administration was 57 hours. In single-dose studies, women had higher exposure to vortioxetine (as measured both by peak concentration and area under the curve), but the differences were small after correcting for weight. The gender difference was not statistically significant in multiple-dose studies. The authors also noted that previous studies had reported that food had no effect on the pharmacokinetics of vortioxetine.

Chen et al[12] carried out multiple studies in healthy human volunteers to evaluate potential pharmacokinetic interactions between vortioxetine and coadministered agents with a range of activity as inhibitors, inducers, or substrates for CYP450 subtypes. They identified potentially significant interactions in the form of increased vortioxetine levels when it was coadministered with bupropion (CYP2D6 inhibitor and CYP2B6 substrate), fluconazole (inhibitor of CYP450 2C9, 2C19, and 3A), and ketoconazole (CYP3A and P-glycoprotein inhibitor) and decreased vortioxetine levels when it was coadministered with rifampicin (CYP inducer). The authors considered that only the interactions with bupropion and rifampicin were likely to be sufficiently significant to warrant possible dosage adjustment. The US datasheet (http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204447s000lbl.pdf) recommends reducing the dose of vortioxetine when giving it in combination with powerful CYP2D6 inhibitors such as bupropion, fluoxetine,

paroxetine, and quinidine, and increasing it when it is administered in combination with powerful CYP inducers such as carbamazepine and phenytoin.

Efficacy studies, including any comparative studies

Animal studies

Animal studies suggest that not only does vortioxetine have an antidepressant-like profile but also that – unlike many established antidepressants – it may have memory-enhancing effects.

The putative antidepressant effects of vortioxetine were confirmed in a behavioral model of depression[13] in which vortioxetine (as well as amitriptyline) significantly reduced immobility in rats in the forced swim test model of induced depression, whereas neither fluoxetine nor duloxetine did so. In keeping with this, Guilloux et al[14] assessed the effects of vortioxetine in three mouse models of anxiety and depression-like behavior – the forced swim test, the open field test, and the novelty-suppressed feeding paradigm. Both acute and repeated dosing with vortioxetine produced antidepressant and anxiolytic effects greater than those produced by fluoxetine and comparable (in the open field test) with those produced by diazepam. Vortioxetine also increased cell proliferation and cell survival of immature granule cells in the dentate gyrus of the hippocampus and stimulated their maturation. These effects were observed despite low levels of serotonin receptor occupancy.

Mørk et al[15] examined the effect of vortioxetine on memory in rats using contextual fear conditioning and novel object recognition tests. They found that vortioxetine enhanced both contextual and episodic memory and that these effects were unrelated to pain sensitivity. They also found that vortioxetine increased extracellular levels of acetylcholine and histamine. They concluded that these effects were consistent with the multiple neurotransmitter effects induced by vortioxetine via 5-HT_3 and 5-HT_7 receptor antagonism and 5-HT_{1A} receptor agonism. In keeping with this, du Jardin et al[16] found that vortioxetine dose-dependently reversed memory deficits in female Long–Evans rats (as measured by object recognition and Y-maze spontaneous alternation tests) induced by 5-HT depletion.

Clinical studies

Vortioxetine has been extensively evaluated as a potential treatment for major depression. We have identified five placebo-controlled short-term (6–8 weeks) studies of vortioxetine in younger adult patients with major depression. Of these, three also had an active comparator (duloxetine or venlafaxine). In addition there has been an acute placebo-controlled study in the elderly and two longer-term relapse prevention studies (one of them randomized and placebo-controlled). Vortioxetine has also been subjected to randomized controlled comparison with agomelatine.

Baldwin et al[17] compared vortioxetine (2.5 mg, 5 mg, or 10 mg) with placebo (with duloxetine 60 mg as an active comparator) in 766 patients with major depression and a Montgomery–Åsberg Depression Rating Scale (MADRS) score of at least 26. On the predefined (last observation carried forward) primary analysis, the differences between vortioxetine (or duloxetine) and placebo were not significant. In mixed model repeat measures analyses however, the two higher doses of vortioxetine were significantly superior to placebo, as was duloxetine.

Mahableshwarkar et al[18] evaluated the safety and efficacy of vortioxetine (2.5 mg or 5 mg) against placebo and against the active comparator duloxetine (60 mg) in an 8-week study in a total of 611 participants. The primary outcome variable was the change from baseline in the 24-item Hamilton Depression Scale (HAMD-24). For vortioxetine, although there was substantial reduction in the HAMD-24 scores, the difference against placebo was not statistically significant for either dose. In contrast, duloxetine showed superiority from placebo at 8 weeks (and also at 6 weeks). Vortioxetine was well-tolerated with low dropout and side-effect rates.

Jain et al[19] randomized 600 people to 5 mg vortioxetine or placebo in a 6-week study. Participants were required to have a MADRS score of at least 30 and a diagnosis of a major depressive episode. The primary endpoints were change from baseline in HAMD-24 total score at 6 weeks and sequential change week by week in HAMD-24 score. Four hundred eighty (80%) participants completed the study. Withdrawal rates (both for adverse events and for lack of efficacy) were similar for vortioxetine and for placebo. There were no significant differences between vortioxetine and placebo in either of the primary outcome variables, though post hoc analyses revealed greater improvement on vortioxetine in the subgroup with high baseline anxiety scores.

Alvarez et al[20] evaluated vortioxetine (5 mg or 10 mg fixed dose) in a 6-week comparison against placebo, with venlafaxine (225 mg slow release) as an active comparator. The primary outcome variable was mean change in MADRS total score. Both doses of vortioxetine were significantly superior to placebo at the 6-week endpoint, with mean MADRS differences from placebo of 5.9 for 5 mg and 5.7 for 10 mg. Venlafaxine was also superior to placebo (mean difference in

6-week MADRS score of 6.4). Secondary outcome measures (response rates as measured by HAMD-24 and MADRS) also showed superiority for both doses of vortioxetine (and for venlafaxine) against placebo.

The efficacy of vortioxetine (at doses of 1 mg, 5 mg, and 10 mg a day) against placebo was evaluated by Henigsberg et al[21] in an 8-week trial involving a total of 560 participants. Participants fulfilled *Diagnostic and Statistical Manual of Mental Disorders* Fourth Edition Text Revision criteria for major depressive episode and had a minimum MADRS score of 26. The highest dose of vortioxetine (10 mg) was significantly superior to placebo on the primary endpoint measure, reduction from baseline in the HAMD-24 total score at week 8 ($P<0.001$). There were also greater improvements with all doses of vortioxetine than with placebo for most depression-related variables.

In a 12-week flexible dose study[22] in 493 patients with MDD who had failed to respond adequately to a selective serotonin reuptake inhibitor or a serotonin-norepinephrine reuptake inhibitor (SNRI), vortioxetine (10–20 mg) was found to be superior to agomelatine (25–50 mg). Change in MADRS total score at 8 weeks was the primary outcome measure. Vortioxetine also showed superiority in several secondary outcome measures.

In a three-arm comparison with duloxetine (60 mg) and placebo over 8 weeks in patients aged 65 and over, vortioxetine (5 mg fixed dose) showed significantly greater improvement than placebo on the predefined primary efficacy endpoint (ie, analysis of covariance, last observation carried forward) of HAMD-24 score at week 8.[23] Duloxetine was also superior to placebo at week 8. Vortioxetine also showed superiority to placebo in a range of cognitive tests (processing speed, verbal learning, and memory), in keeping with the findings from animal studies.

It is perhaps noteworthy that in three of the above studies,[18,20,23] although formal statistical comparison between active drugs was not reported, there was a trend for the SNRI active comparator to be associated with numerically superior outcomes to vortioxetine.

In common with other antidepressants, vortioxetine appears to be effective in preventing depressive relapse. Baldwin et al[24] reported on a 52-week, open-label extension study which followed an 8-week lead-in. The MADRS total score was used as the primary outcome variable. In total, 328/535 patients (61.3%) completed the study, representing a total of 393 patient years of exposure to vortioxetine. At the point of entry to the extension study, participants had a mean MADRS total score of 13.5±8.7. During the subsequent year, the mean MADRS total score in completers decreased by approximately 8 points to 5.5±6.0 at week 52 (OC) and the proportion of responders rose from 63% to 94%. Remission rate in completers (42% at the start of the study) had increased to 83% (OC). Relapse rate in those in remission at the start of the study (n=226) was 9.7%.

Boulenger et al[25] confirmed that vortioxetine was effective in preventing depressive relapse in a study of 396 patients who, after achieving remission during 12-weeks of open-label treatment with 5–10 mg vortioxetine, were randomized to either placebo or vortioxetine (fixed dose of 5 mg or 10 mg as determined during the open-label phase). The primary efficacy variable was time to relapse (defined on the basis of a MADRS score of >21 or clinically judged lack of efficacy). Overall, fewer patients (13% versus 26%) relapsed on vortioxetine than on placebo ($P=0.013$). Nausea was the only side effect that occurred significantly more often with vortioxetine than with placebo during the double-blind phase of the study.

Safety and tolerability

Clinical studies suggest that vortioxetine has a good safety and tolerability profile. Henigsberg et al[21] reported that vortioxetine was generally well-tolerated; the most common adverse events associated with it were nausea, headache, and dizziness. Alvarez et al[20] noted higher adverse-event-related withdrawal rates on venlafaxine (14%) than for either dose of vortioxetine (3% on 5 mg and 7% on 10 mg) or for placebo (4%). Sexual dysfunction on vortioxetine was at a similar rate to that found on placebo. In keeping with this, Baldwin et al[17] reported sexual dysfunction was present in very few participants (2%–4%) at all three vortioxetine doses they studied, compared with 14% of those on duloxetine. In their comparison with agomelatine, Häggström et al[22] found that vortioxetine was better tolerated overall (adverse-event-related withdrawal dates of 5.9% versus 9.5%). Vortioxetine is also well-tolerated in older people. Katona et al[23] found that the adverse-event-related withdrawal rates were 5.8% for vortioxetine compared with 2.8% (placebo) and 9.9% (duloxetine). Nausea was the only adverse event with a significantly higher incidence on vortioxetine (21.8%) than placebo (8.3%). In contrast, the incidence of nausea, constipation, dry mouth, hyperhidrosis, and somnolence were all higher for duloxetine than placebo.

Vortioxetine appears not to affect driving performance. Theunissen et al[26] examined its effects (at a dose of 10 mg/day) on driving, cognitive, and psychomotor performance (in a randomized controlled comparison with mirtazapine 30 mg/day and placebo) in 24 healthy subjects over a 15-day period. Vortioxetine did not cause any impairment in any of

the measures at either of the time points (day 2 and day 16 – ie, the morning after the last dose). In contrast, mirtazapine (which is of course relatively sedating) was associated with cognitive and psychomotor impairment on day 2, but this was no longer apparent on day 16.

Conclusion and place in therapy

Vortioxetine represents a new class of antidepressant. It has multiple actions that enhance serotonergic activity. This appears to have "knock-on" effects on other neurotransmitters implicated in the causation and maintenance of depressive disorders. Vortioxetine is well-tolerated and appears to have relatively little potential for adverse drug interactions. Clinical studies indicate that it is effective in the treatment of major depression. Though there is no suggestion of superiority over active comparators (and some suggestion that SNRIs may show greater efficacy), most studies suggest that there is a clinically meaningful advantage in terms of tolerability. Incidence of sexual side-effects appears particularly low. Older people tolerate vortioxetine well, and there is some evidence that it may have cognitive benefits.

Disclosure

Cornelius L Katona is currently involved in a clinical trial of vortioxetine and has given paid talks and received payments for consultancy work by Lundbeck. Cara P Katona has no potential conflicts of interest.

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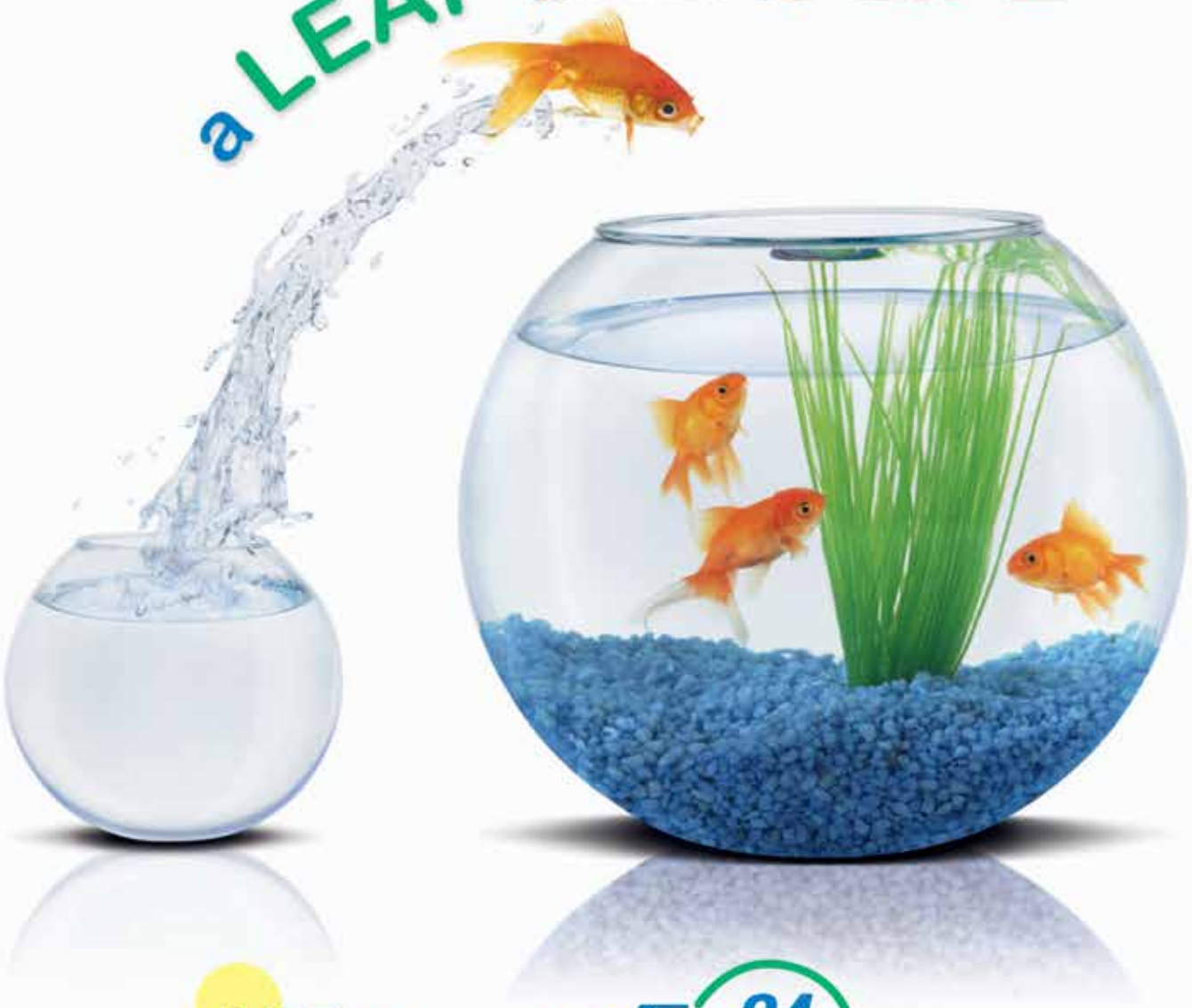

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