Augmentation of olanzapine in treatment-resistant schizophrenia

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Objective: Up to 40% of patients with schizophrenic psychoses have symptoms that are resistant to monotherapy with antipsychotic drugs. In consequence, combinations of drugs are often used, especially based on the antipsychotic agents clozapine and olanzapine because of their broad receptor-interaction profile. The aim of this review was to provide a critical overview of the published results of olanzapine augmentation. **Methods:** A systematic database search was performed of MEDLINE and BIOSIS (Ovid), looking for publications on augmented therapeutic approaches involving olanzapine. The search terms used were "augmentation," "combination," "schizophrenia," "olanzapine," and the names of other antipsychotic drugs and non-antipsychotic agents, including brand names, spanning publications from 1966 until the end of December 2004. **Results:** Of 14 reports dealing with 8 different antipsychotic augmentation strategies (83 patients), only 1 trial, of sulpiride–olanzapine therapy, was performed in a randomized manner. Based on clinical observation, a significant number of the treatments led to favourable results. In contrast to adjuvant therapy with antipsychotic drugs, augmentation of olanzapine with glycine, antidepressants or mood stabilizers was evaluated in well-designed clinical trials (8 publications, 989 patients), with distinct improvements of positive and/or negative symptoms reported. **Conclusions:** The combination of olanzapine with antidopaminergic atypical antipsychotic agents seems to follow a neurobiological rationale. The augmentation trials with non-antipsychotic agents, for example, mood stabilizers, were successful and showed that randomized and placebo-controlled trials are feasible. Therefore, systematic evaluations of antipsychotic agents as adjuvant therapy are possible as well as necessary to determine the benefits and risks of any new treatment strategy.

Objectif : Jusqu'à 40 % des malades atteints de psychoses schizophréniques présentent des symptômes qui résistent à la monothérapie aux antipsychotiques. Par conséquent, on administre souvent des combinaisons de médicaments, basées particulièrement sur les agents antipsychotiques clozapine et olanzapine, en raison de leur large profil récepteur-interaction. L'objet de cet examen consistait à présenter une vue d'ensemble critique des résultats publiés de l'augmentation de l'olanzapine. **Méthodes :** Une recherche systématique a été effectuée dans les bases de données MEDLINE et BIOSIS (Ovid) pour trouver des publications sur les approches thérapeutiques à posologie augmentée comportant de l'olanzapine. Les termes de recherche utilisés étaient « augmentation », « combination », « schizophrenia », « olanzapine » et le nom d'autres agents antipsychotiques et non antipsychotiques, comprenant des noms de marque, couvrant des publications de 1966 jusqu'à la fin de décembre 2004. **Résultats :** Sur 14 rapports traitant de 8 différentes stratégies d'augmentation d'antipsychotiques (83 patients), un seul essai portant sur la thérapie à la sulpiride–olanzapine a été effectué de façon randomisée. Selon l'observation clinique, un nombre significatif des traitements ont produit des résultats favorables. Contrairement à la thérapie auxiliaire aux antipsychotiques, l'augmentation d'olanzapine avec de la glycine, des antidépresseurs ou des régulateurs de l'humeur a été évaluée dans le cadre d'essais cliniques bien conçus (8 publications, 989 patients), et faisait état d'améliorations nettes des symptômes positifs et(ou) négatifs signalés. **Conclusions :** La combinaison d'olanzapine avec des antipsychotiques atypiques antidopaminergiques semble répondre à une logique neurobiologique. Les essais d'augmentation avec des agents non antipsychotiques, par exemple, des régulateurs de l'humeur, ont produit des résultats favorables et montré que des essais randomisés et contrôlés sont réalisables. Par conséquent, des évaluations systématiques des agents antipsychotiques comme thérapie auxiliaire sont possibles et même nécessaires pour déterminer les avantages et les risques de toute nouvelle stratégie de traitement.

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Introduction

Antipsychotic substances markedly improve therapy and prognosis for patients with schizophrenic psychoses,[1] which before the advent of these compounds were considered to be severe and devastating psychiatric disorders. However, a large number of the so-called typical antipsychotic agents can cause severe extrapyramidal motoric symptoms and other side effects.[2] Moreover, up to 40% of patients with psychotic symptoms do not respond to conventional antipsychotic therapy.[3] Clozapine, representing a second generation of so-called atypical antipsychotic drugs, has shown positive effects in cases of formerly treatment-resistant psychoses.[4,5] However, its use is limited because of major side effects including potentially lethal agranulocytosis.[6,7] Within the heterogeneous group of atypical antipsychotics, the thienobenzodiazepine derivative olanzapine has a receptor profile that is quite similar to that of clozapine, as indicated by having a greater affinity for serotonergic 5-HT_{2A} receptors than for dopaminergic D_2 receptors.[8,9] The positive and negative symptoms of schizophrenic psychoses usually respond well to this drug.[10,11] In contrast to clozapine, olanzapine does not induce major agranulocytosis but may, in a significant number of cases, lead to bothersome side effects including significant weight gain, sedation, anticholinergic effects and transient increases of liver enzymes.[12]

Faced with a partial response to antipsychotic monotherapy or because of side effects that might interfere with a patient's compliance, clinicians often use a combination of several drugs.[13,14] In particular, clozapine has been used in various combined treatment settings, as recently reviewed.[15,16] Evidence for superior efficacy and tolerability exists for the combinations of clozapine with sulpiride,[17] amisulpride[18,19] and risperidone.[20,21] Nevertheless, the widespread clinical practice of augmentation strategies stands in contrast to the scarce evidence derived in most cases from open-labelled, retrospective studies.[22,23] In particular, a recent investigation compared cohorts treated with antipsychotic monotherapy or polytherapy that had, initially, not displayed differences in diagnosis, age and severity of illness scores.[24] The authors reported higher cumulative doses, more side effects and a longer treatment period in the polytherapy group.

Because of positive clinical experiences regarding the combination of amisulpride and olanzapine,[25] I embarked on this review with the goal of systematically evaluating reports of combinations of olanzapine with other psychotropic substances.

Methods

A systematic database search was performed of MEDLINE and BIOSIS (Ovid) using the search terms "augmentation," "combination," "schizophrenia," "olanzapine," and the names of the other substances listed in Table 1[26–37] and Table 2,[38–45] including brand names, spanning publications from 1966 until the end of December 2004.

Results

This literature search resulted in 14 reports on the combined use of olanzapine and other antipsychotic substances. In addition, 8 reports on augmentation strategies that did not involve antipsychotic agents were retrieved. Among the publications on antipsychotic augmentation (Table 1), only 1 randomized trial was performed, regarding the combination of olanzapine and sulpiride.[35] Two studies had an open prospective design,[32,34] with the remaining majority characterized as case reports or retrospective chart reviews. The treatments of a total of 83 patients diagnosed with psychotic disorders such as schizophrenia or schizoaffective disorder, mostly based on the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV), are documented (haloperidol $n = 40$, fluphenazine $n = 1$, pimozide $n = 1$, clozapine $n = 3$, risperidone $n = 6$, sulpiride $n = 23$, amisulpride $n = 8$, and aripiprazole $n = 1$). The treatment duration and monitoring varied significantly, ranging from a few days to 2 years. The daily dose of olanzapine ranged from 7.5 mg to 30 mg, with an average of 22.2 mg/d, calculated by averaging all reported doses by the combined total sample sizes. Therapeutic effects were evaluated by applying psychometric scales such as the Brief Psychiatric Rating scale (BPRS) or the Positive and Negative Syndrome scale (PANSS). However, in some cases, only clinical observations were performed to evaluate the outcome. In contrast to most of the studies, which reported favourable treatment results, the randomized trial using sulpiride[35] failed to achieve a significant amelioration of psychotic symptoms; the affective state, however, improved. In addition, several case reports documented important side effects such as neutropenia[27] and malignant neuroleptic syndrome as a consequence of using haloperidol as an adjuvant treatment.[26] However, improvements in pre-existing side effects were reported.[25] Interestingly, none of these publications evaluated the economic consequences of combined pharmacotherapy.

Because of unsatisfactory treatment responses to olanzapine, a number of non-antipsychotic substances were used as alternative add-ons (Table 2). Four of these investigations were designed as double-blind, placebo-controlled trials,[39,40,42,43] 1 as a retrospective case series[44] and the remaining 3 as open prospective trials. Altogether 989 patients were evaluated. Most of these patients were enrolled in augmentation studies with divalproex and valproic acid; a much smaller number were enrolled in augmentation studies with topiramate, lamotrigine, glycine, reboxetine or fluvoxamine. The monitoring period ranged from 4 weeks to 12 months, and the daily dose of olanzapine ranged from 7.3 mg to 43.3 mg, with an average of 10.8 mg/d, calculated by averaging all reported doses by the combined total sample sizes. Treatment response was assessed using psychometric scales such as BPRS, the Scale for the Assessment of Negative Symptoms (SANS) and PANSS, but never exclusively based on clinical impressions. In contrast to antipsychotic augmentations, only limited improvement on psychotic symptoms was achieved with the non-antipsychotic substances, for example, by addressing the hostility item of the PANSS rating scale. In addition, side effects of this combined therapy were absent or of minor importance. The economic consequences of this type of polypharmacy were not evaluated.

Table 1: Published reports (*n* = 14) describing the combined use of olanzapine and another antipsychotic agent

Antipsychotic agent used with olanzapine	Reference	Study design	Diagnosis	Period of monitoring	No. of patients	Indication for combined therapy	Dose, mg/d		Effects as evaluated by psychometric scales	Side effects
							Olanzapine	Other agent		
Haloperidol	Mujica and Weiden[26]	CR	Schizophrenia	3 mo	1	PS	10	23	—	Malignant neuroleptic syndrome
Haloperidol	Abdullah et al[27]	CR	Schizophrenia	8 d	1	PS, hostility	20	10	Not reported	Neutropenia
Haloperidol	McCue et al[13]	RetrCR	Schizophrenia (DSM-IV)	?	38	Not reported	?	?	Not reported	—
Fluphenazine	Tofler and Ahmed[28]	CR	Bipolar disorder with psychotic features	?	1	PS, impulsivity	30	20	Not reported	Malignant neuroleptic syndrome
Pimozide	Takhar[29]	CR	Disorganized schizophrenia (DSM-IV)	24 mo	1	Treatment resistance	20	3	BPRS improved by 40%	—
Clozapine	Gupta et al[30]	CR	Schizophrenia, schizoaffective disorder (DSM-IV)	24 wk	2	Treatment resistance	15	600 and 250	BPRS improved by 35%	—
Clozapine	Rhoads[31]	CR	Schizoaffective disorder	18 mo	1	Treatment resistance, side effects	10	100	Improved PS	—
Risperidone	Lerner et al[32]	OPrT	Schizophrenia, schizoaffective disorder (DSM-IV)	?	5	Treatment resistance to monotherapy	10–15	1–5	BPRS improved by 25%–38%	—
Risperidone	Seger and Lamberti[33]	CR	Schizophrenia, obsessive–compulsive disorder (DSM-IV)	4 mo	1	Treatment resistance	7.5	6	Improvement of schizophrenia + obsessive–compulsive disorder	Priapism
Sulpiride	Raskin et al[34]	OPrT	Schizophrenia (DSM-IV)	10 wk	6	Treatment resistance	27	377	BPRS improved by 37.25%, PANSS by 32.67%	—
Sulpiride	Kotler et al[35]	RandT	Schizophrenia (DSM-IV)	8 wk	17	Treatment resistance, PANSS ≥ 100	22.2	600	HAM-D improved significantly, but no changes in PANSS, HAM-A	SAS, BAS unchanged
Amisulpride	Pedrosa Gil et al[36]	CR	Schizophrenia, multisystemic myotonic myopathy	3 mo	1	PS	10	200	Complete remission	Increase of CK to 1867 U/L
Amisulpride	Zink et al[25]	RetrCR	Schizophrenia (ICD-10, DSM-IV)	Several wk	7	PS, NS, EPMS	21.4 (reduced by 21%*)	485.7 (reduced by 26%*)	Improvement of PS and NS, GAF increase by 29%, CGI from 5.9 to 3.6	Weight gain: 6.2 kg
Aripiprazole	Duggal[37]	CR	Schizophrenia	5 mo	1	NS	20	15	PANSS improved by 50% (PS), 69% (NS), 45% GP	—

Note: BAS = Barnes Akathisia scale; BPRS = Brief Psychiatric Rating scale; CGI = Clinical Global Impression scale (severity of illness); CK = creatine kinase; CR = case report; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition; EPMS = extrapyramidal motoric symptoms; GAF = Global Assessment of Functioning scale; GP = global psychpathology; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems*; NS = negative symptoms; OPrT = open prospective trial; PANSS = Positive and Negative Syndrome Scale; PS = positive symptoms; RandT = randomized trial; RetrCR = retrospective chart review; SAS = Simpson–Angus scale.
*Compared with monotherapy.

Discussion

The combination of olanzapine with other psychotropic substances is a therapeutic strategy that is used quite often in cases of treatment-resistant schizophrenic psychoses. However, because of the limited findings on augmentations with antipsychotic agents, further clinical trials are necessary to evaluate the risks and benefits.

The atypical antipsychotic substance olanzapine has been in common use in the therapy of psychiatric disorders other

Table 2: Published reports (*n* = 8) describing the combined use of olanzapine and a non-antipsychotic agent

Non-antipsychotic agent used with olanzapine	Reference	Study design	Diagnosis	Period of monitoring	No. of patients	Indication for combined therapy	Dose, mg/d		Effects as evaluated by psychometric scales	Side effects
							Olanzapine	Other agent		
Fluvoxamine	Hiemke et al[38]	OT	Schizophrenia	8 wk	8	Research with regard to metabolism	10–20	100	SANS improved by ≥ 20% in 5 of 7 cases	Serum olanzapine concentration increased by 12%–112%. No other side effects
Reboxetine	Poyurovsky et al[39]	DbPlacT	Schizophrenia (DSM-IV)	6 wk	26	Weight gain	10	4	Antidepressive effect in the treatment group (HAM-D)	Significantly less weight gain in the treatment group
Glycine	Heresco-Levy et al[40]	DbPlacT	Schizophrenia (DSM-IV)	6 wk	12	Treatment resistance	14.3 (SD 6.2)	800 mg/kg/d	Improved NS (improved PS)	Upper gastrointestinal discomfort
Lamotrigine	Dursun and Deakin[41]	OT	Schizophrenia (DSM-IV)	24 wk	3	Treatment resistance (BPRS ≥ 30)	43.3 (SD 5.8)	100–300	No significant change of BPRS	No side effects
Topiramate	Dursun and Deakin[41]	OT	Schizophrenia (DSM-IV)	24 wk	3	Treatment resistance (BPRS ≥ 30)	33.3 (SD 5.7)	225–300	No significant change of BPRS	No side effects
Divalproex	Casey et al[42]	DbPlacT	Schizophrenia (DSM-IV)	4 wk	131	Acute exacerbation (PANSS ≥ 60)	15	2364	Superiority of combined therapy (PANSS, BPRS)	Side effects not different
Divalproex	Citrome et al[43]	DbPlacT	Schizophrenia (DSM-IV)	4 wk	249*	Acute exacerbation (PANSS ≥ 60)	15	2363	Hostility item (PANSS) in combination improved.† Frequency of lorazepam use not different	Abnormal liver function, asthma, hyperglycemia, rash
Valproate	Cramer and Sernyak[44]	RetrCR	Chronic psychotic disorder assumed	270 d	547	Insufficient response	7.3 (SD 3.6)	411.6	Significantly longer treatment persistence‡ in combination as compared with olanzapine monotherapy (127 d v. 159 d)	Not reported
Valproate	Litrell et al[45]	OT	Schizophrenia (DSM-IV)	12 mo	10	Treatment resistance	19 (SD 6.6)	750–2000 (serum level 50–100 µg/mL)	Reduced hostility (PANSS) in combination	Weight gain

Note: BPRS = Brief Psychiatric Rating scale; DbPlacT = double-blind, placebo-controlled trial; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition; HAM-D = Hamilton Rating Scale for Depression; NS = negative symptoms; OT = open trial; PANSS = Positive and Negative Syndrome scale; PS = positive symptoms; RetrCR = retrospective chart review; SANS = Scale for the Assessment of Negative Symptoms; SD = standard deviation.
*Subgroups: olanzapine + placebo (*n* = 65), olanzapine + divalproex (*n* = 66), risperidone + placebo (*n* = 60), risperidone + divalproex (*n* = 58). In total, 166 completers including cohorts treated with risperidone.
†As assessed at days 3 and 7, not significant at days 5,10,14,21 and 28.
‡Kaplan–Meier curve.

than schizophrenia and, more specifically, combinations with olanzapine were reported with the serotonin reuptake inhibitor (SSRI) fluoxetine in the treatment of borderline personality disorder,[46] with topiramate for bipolar disorder,[47] with fluoxetine for obsessive–compulsive disorder[48,49] and again with the same SSRI for depression.[50–53] The latter combination was additionally investigated in biological models at a molecular level.[54–57]

Olanzapine combinations have been prescribed to patients with treatment-resistant schizophrenic psychoses, and they are the focus of this review. Usually, treatment-resistant psychoses prompt the clinician to either switch to another monotherapy or add onto the pre-existing strategy in order to augment the pharmacological profile. In this context, it may be important to note that a recent survey detected insufficient treatment responses of positive symptoms as the main reason for applying an augmented antipsychotic therapy.[58] As an alternative, switching to clozapine monotherapy would be wise, because this substance is known to be effective in formerly treatment-resistant psychoses,[4,5] and more so than olanzapine.[59] If clinicians prefer augmentation strategies with olanzapine, which is a substance with complex pharmacodynamic and pharmacokinetic interactions due to metabolism via the cytochrome P450 system,[60,61] the importance of therapeutic drug monitoring has to be emphasized.[62,63]

A significant number of substances have been used in combination with olanzapine, mirroring the increased incidence of these approaches. This fact is underscored by an investigation in the United States where McCue et al counted not even 1 antipsychotic combination in a representative cohort of 454 patients in 1995. This is in contrast to 93 combinations used among 583 patients in 2001.[13] Although 38 patients were treated in that sample with haloperidol and olanzapine, a solid evaluation of this specific combination was not possible because of the lack of pharmacological and clinical data. Therefore, the main clinical question remains to be answered: What benefit may be expected from these treatments in the light of risks such as malignant neuroleptic syndromes[26,28] and neutropenia[27] in combination therapy with haloperidol or fluphenazine or priapism in augmentation with risperidone?[33]

Even the efficacy of this strategy regarding treatment-resistant positive symptoms has to be questioned: the only randomized trial, dealing with sulpiride augmentation, failed to achieve significant improvements on the PANSS scale.[35] In contrast to this negative result, favourable experiences have been reported after augmentation with sulpiride,[34] the closely related D_2/D_3-antagonistic benzamide amisulpride,[25] aripiprazole[37] or risperidone.[32] One might be tempted to formulate the hypothesis that an additional antidopaminergic receptor interaction increases the benefits of an olanzapine-based therapy. Yet another hypothesis should be tested in the future, namely, augmentation with sulpiride[35] or aripiprazole[37] has resulted in improvements of negative symptoms and of depressed mood: Is it therefore possible to include an additional antidepressive component as part of therapy using antidopaminergic augmentation?

Antipsychotic augmentation ought to be compared with non-antipsychotic drugs as adjuvant therapy to olanzapine. The indication for these latter studies did not significantly differ from those for the studies of augmentation with antipsychotic agents. Only 10.8 mg of olanzapine were used in these studies, which is half of the dose applied in antipsychotic augmentations. In these latter studies, 989 patients were evaluated after augmentation with fluvoxamine, reboxetine, glycine, lamotrigine, topiramate, divalproex and valproic acid, that is, about 10 times the number of patients as compared with the antipsychotic augmentations. Moreover, these investigations followed a design of double-blind, placebo-controlled trials or at least open prospective studies and assessed the target effects with established psychometric scales. With the exception of lamotrigine and topiramate augmentation,[41] significant improvements of negative (fluvoxamine, glycine) and positive (divalproex, valproic acid) symptoms as well as side effects (reboxetine) were achieved.

A further comparison is necessary: the augmentation of clozapine with atypical antipsychotic substances[16] may be considered an equally difficult topic in clinical research. Nevertheless, several double-blind placebo-controlled trials have been performed,[17,20,21] and reports describing about 1300 treated patients have been published. Furthermore, the pharmacodynamic consequences of antidopaminergic augmentation of clozapine have been investigated with the tools of nuclear medicine[64,65]

In conclusion, this review of augmented olanzapine therapies may be of assistance in defining scientific needs but to a lesser extent in providing suggestions with regard to the clinician's daily work, although the augmentation with valproic acid might be considered in reducing symptoms of hostility. Furthermore, the antidopaminergic augmentations with sulpiride or amisulpride follow a neurobiological rationale. However, further well-designed clinical investigations are necessary in the future. These trials can be performed, as illustrated, with antipsychotic augmentations of clozapine or non-antipsychotic augmentations of olanzapine. Optimally, they could lead to an estimation of the risks and benefits of olanzapine augmentation strategies and a ranking of the various alternatives.

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References

1. Lieberman JA, Golden R, Stroup S, McEvoy J. Drugs of the psychopharmacological revolution in clinical psychiatry. *Psychiatr Serv* 2000;51:1254-8.

2. Sethi KD. Movement disorders induced by dopamine blocking agents. *Semin Neurol* 2001;21(1):59-68.

3. Hellewell JS. Treatment-resistant schizophrenia: reviewing the options and identifying the way forward. *J Clin Psychiatry* 1999;60 (Suppl 23):14-9.

4. Young CR, Longhurst JG, Bowers MB Jr, Mazure CM. The expanding indications for clozapine. *Exp Clin Psychopharmacol* 1997;5:216-34.

5. Buchanan RW. Clozapine: efficacy and safety. *Schizophr Bull* 1995; 21:579-91.

6. Young CR, Bowers MB Jr, Mazure CM. Management of the adverse effects of clozapine. *Schizophr Bull* 1998;24:381-90.

7. Miller DD. Review and management of clozapine side effects. *J Clin Psychiatry* 2000;61(Suppl 8):14-7[discussion 18-9].

8. Stephenson CM, Pilowsky LS. Psychopharmacology of olanzapine. A review. *Br J Psychiatry Suppl* 1999;(38):52-8.

9. Meltzer HY, McGurk SR. The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. *Schizophr Bull* 1999;25:233-55.

10. Bhana N, Foster RH, Olney R, Plosker GL. Olanzapine: an updated review of its use in the management of schizophrenia. *Drugs* 2001;61:111-61.

11. Duggan L, Fenton M, Dardennes RM, El-Dosoky A, Indran S. Olanzapine for schizophrenia. *Cochrane Database Syst Rev* 2000;(2): CD001359.

12. Conley RR, Meltzer HY. Adverse events related to olanzapine. *J Clin Psychiatry* 2000;61(Suppl 8):26-9[discussion 30].

13. McCue RE, Waheed R, Urcuyo L. Polypharmacy in patients with schizophrenia. *J Clin Psychiatry* 2003;64:984-9.

14. Grohmann R, Engel RR, Geissler KH, Ruther E. Psychotropic drug use in psychiatric inpatients: recent trends and changes over time-data from the AMSP study. *Pharmacopsychiatry* 2004;37(Suppl 1): S27-38.

15. Lerner V, Libov I, Kotler M, Strous RD. Combination of "atypical" antipsychotic medication in the management of treatment-resistant schizophrenia and schizoaffective disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2004;28:89-98.

16. Zink M, Dressing H. Augmentation of clozapine with atypical antipsychotic substances. *Curr Psychiatry Rev* 2005;1(2):165 -72.

17. Shiloh R, Zemishlany Z, Aizenberg D, Radwan M, Schwartz B, Dorfman-Etrog P, et al. Sulpiride augmentation in people with schizophrenia partially responsive to clozapine. A double-blind, placebo-controlled study. *Br J Psychiatry* 1997;171:569-73.

18. Zink M, Knopf U, Henn FA, Thome J. Combination of clozapine and amisulpride in treatment-resistent schizophrenia - case reports and review of the literature. *Pharmacopsychiatry* 2004;37:26-31.

19. Munro J, Matthiasson P, Osborne S, Travis M, Purcell S, Cobb AM, et al. Amisulpride augmentation of clozapine: an open non-randomized study in patients with schizophrenia partially responsive to clozapine. *Acta Psychiatr Scand* 2004;110:292-8.

20. Josiassen RC, Joseph A, Kohegyi E, Stokes S, Dadvand M, Paing WW, et al. Clozapine augmented with risperidone in the treatment of schizophrenia: a randomized, double-blind, placebo-controlled trial. *Am J Psychiatry* 2005;162:130-6.

21. Anil Yagcioglu AE, Kivircik Akdede BB, Turgut TI, Tumuklu M, Yazici MK, Alptekin K, et al. A double-blind controlled study of adjunctive treatment with risperidone in schizophrenic patients partially responsive to clozapine: efficacy and safety. *J Clin Psychiatry* 2005;66:63-72.

22. Stahl SM. Antipsychotic polypharmacy: evidence based or eminence based? *Acta Psychiatr Scand* 2002;106:321-2.

23. Freudenreich O, Goff DC. Antipsychotic combination therapy in schizophrenia. A review of efficacy and risks of current combinations. *Acta Psychiatr Scand* 2002;106:323-30.

24. Centorrino F, Goren JL, Hennen J, Salvatore P, Kelleher JP, Baldessarini RJ. Multiple versus single antipsychotic agents for hospitalized psychiatric patients: case-control study of risks versus benefits. *Am J Psychiatry* 2004;161:700-6.

25. Zink M, Henn FA, Thome J. Combination of amisulpride and olanzapine in treatment-resistant schizophrenic psychoses. *Eur Psychiatry* 2004;19:56-8.

26. Mujica R, Weiden P. Neuroleptic malignant syndrome after addition of haloperidol to atypical antipsychotic. *Am J Psychiatry* 2001; 158:650-1.

27. Abdullah N, Voronovitch L, Taylor S, Lippmann S. Olanzapine and haloperidol: Potential for neutropenia? *Psychosomatics* 2003;44:83-4.

28. Tofler IT, Ahmed B. Atypical (olanzapine) plus conventional (fluphenazine) neuroleptic treatment associated with the neuroleptic malignant syndrome. *J Clin Psychopharmacol* 2003;23:672-4.

29. Takhar J. Pimozide augmentation in a patient with drug-resistant psychosis previously treated with olanzapine. *J Psychiatry Neurosci* 1999;24:248-9.

30. Gupta S, Sonnenberg SJ, Frank B. Olanzapine augmentation of clozapine. *Ann Clin Psychiatry* 1998;10:113-5.

31. Rhoads E. Polypharmacy of 2 atypical antipsychotics. *J Clin Psychiatry* 2000;61:678-80.

32. Lerner V, Chudakova B, Kravets S, Polyakova I. Combined use of risperidone and olanzapine in the treatment of patients with resistant schizophrenia: a preliminary case series report. *Clin Neuropharmacol* 2000;23:284-6.

33. Seger A, Lamberti JS. Priapism associated with polypharmacy. *J Clin Psychiatry* 2001;62:128.

34. Raskin S, Durst R, Katz G, Zislin J. Olanzapine and sulpiride: a preliminary study of combination/augmentation in patients with treatment-resistant schizophrenia. *J Clin Psychopharmacol* 2000;20: 500-3.

35. Kotler M, Strous RD, Reznik I, Shwartz S, Weizman A, Spivak B. Sulpiride augmentation of olanzapine in the management of treatment-resistant chronic schizophrenia: evidence for improvement of mood symptomatology. *Int Clin Psychopharmacol* 2004;19:23-6.

36. Pedrosa Gil F, Schneider C, Grohmann R, Ruther E. Incompatibility of olanzapine and amisulpride in multisystemic myotonic myopathy [published erratum appears in *Nervenarzt* 2001;72:878]. *Nervenarzt* 2001;72(9):729-33. German.

37. Duggal HS. Aripirazole-olanzapine combination for treatment of schizophrenia. *Can J Psychiatry* 2004;49:151.

38. Hiemke C, Peled A, Jabarin M, Hadjez J, Weigmann H, Hartter S, et al. Fluvoxamine augmentation of olanzapine in chronic schizophrenia: pharmacokinetic interactions and clinical effects. *J Clin Psychopharmacol* 2002;22:502-6.

39. Poyurovsky M, Isaacs I, Fuchs C, Schneidman M, Faragian S, Weizman R, et al. Attenuation of olanzapine-induced weight gain with reboxetine in patients with schizophrenia: a double-blind, placebo-controlled study. *Am J Psychiatry* 2003;160(2):297-302.

40. Heresco-Levy U, Ermilov M, Lichtenberg P, Bar G, Javitt DC. High-dose glycine added to olanzapine and risperidone for the treatment of schizophrenia. *Biol Psychiatry* 2004;55:165-71.

41. Dursun SM, Deakin JF. Augmenting antipsychotic treatment with lamotrigine or topiramate in patients with treatment-resistant schizophrenia: a naturalistic case-series outcome study. *J Psychopharmacol* 2001;15:297-301.

42. Casey DE, Daniel DG, Wassef AA, Tracy KA, Wozniak P, Sommerville KW. Effect of divalproex combined with olanzapine or

risperidone in patients with an acute exacerbation of schizophrenia. *Neuropsychopharmacology* 2003;28:182-92.

43. Citrome L, Casey DE, Daniel DG, Wozniak P, Kochan LD, Tracy KA. Adjunctive divalproex and hostility among patients with schizophrenia receiving olanzapine or risperidone. *Psychiatr Serv* 2004;55:290-4.

44. Cramer JA, Sernyak M. Results of a naturalistic study of treatment options: switching atypical antipsychotic drugs or augmenting with valproate. *Clin Ther* 2004;26:905-14.

45. Littrell KH, Petty RG, Hilligoss NM, Kirshner CD, Johnson CG. Valproate for hostility in schizophrenia patients. *J Clin Psychiatry* 2004;65:134.

46. Zanarini MC, Frankenburg FR, Parachini EA. A preliminary, randomized trial of fluoxetine, olanzapine, and the olanzapine-fluoxetine combination in women with borderline personality disorder. *J Clin Psychiatry* 2004;65:903-7.

47. Vieta E, Sanchez-Moreno J, Goikolea JM, Colom F, Martinez-Aran A, Benabarre A, et al. Effects on weight and outcome of long-term olanzapine-topiramate combination treatment in bipolar disorder. *J Clin Psychopharmacol* 2004;24:374-8.

48. Shapira NA, Ward HE, Mandoki M, Murphy TK, Yang MC, Blier P, et al. A double-blind, placebo-controlled trial of olanzapine addition in fluoxetine-refractory obsessive-compulsive disorder. *Biol Psychiatry* 2004;55:553-5.

49. Bystritsky A, Ackerman DL, Rosen RM, Vapnik T, Gorbis E, Maidment KM, et al. Augmentation of serotonin reuptake inhibitors in refractory obsessive-compulsive disorder using adjunctive olanzapine: a placebo-controlled trial. *J Clin Psychiatry* 2004;65:565-8.

50. Shelton RC. The combination of olanzapine and fluoxetine in mood disorders. *Expert Opin Pharmacother* 2003;4:1175-83.

51. Rothschild AJ, Williamson DJ, Tohen MF, Schatzberg A, Andersen SW, Van Campen LE, et al. A double-blind, randomized study of olanzapine and olanzapine/fluoxetine combination for major depression with psychotic features. *J Clin Psychopharmacol* 2004;24:365-73.

52. Corya SA, Andersen SW, Detke HC, Kelly LS, Van Campen LE, Sanger TM, et al. Long-term antidepressant efficacy and safety of olanzapine/fluoxetine combination: a 76-week open-label study [published erratum appears in *J Clin Psychiatry* 2004;65(2):279]. *J Clin Psychiatry* 2003;64:1349-56.

53. Tohen M, Vieta E, Calabrese J, Ketter TA, Sachs G, Bowden C, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression [published erratum appears in *Arch Gen Psychiatry* 2004;61(2):176]. *Arch Gen Psychiatry* 2003;60:1079-88.

54. Seager MA, Huff KD, Barth VN, Phebus LA, Rasmussen K. Fluoxetine administration potentiates the effect of olanzapine on locus coeruleus neuronal activity. *Biol Psychiatry* 2004;55:1103-9.

55. Ordway GA, Szebeni K. Effect of repeated treatment with olanzapine or olanzapine plus fluoxetine on tyrosine hydroxylase in the rat locus coeruleus. *Int J Neuropsychopharmacol* 2004;7:321-7.

56. Maragnoli ME, Fumagalli F, Gennarelli M, Racagni G, Riva MA. Fluoxetine and olanzapine have synergistic effects in the modulation of fibroblast growth factor 2 expression within the rat brain. *Biol Psychiatry* 2004;55:1095-102.

57. Horowitz JM, Goyal A, Ramdeen N, Hallas BH, Horowitz AT, Torres G. Characterization of fluoxetine plus olanzapine treatment in rats: a behavior, endocrine, and immediate-early gene expression analysis. *Synapse* 2003;50:353-64.

58. Sernyak MJ, Rosenheck R. Clinicians' reasons for antipsychotic coprescribing. *J Clin Psychiatry* 2004;65:1597-600.

59. Kelly DL, Richardson CM, Tamminga CA, Carpenter WT. The efficacy of high-dose olanzapine versus clozapine in treatment-resistant schizophrenia: a double-blind, crossover study. *J Clin Psychopharmacol* 2003;23:668-70.

60. Ring BJ, Binkley SN, Vandenbranden M, Wrighton SA. In vitro interaction of the antipsychotic agent olanzapine with human cytochromes p450 CYP2C9, CYP2C19,CYP2D6 and CYP3A. *Br J Clin Pharmacol* 1996;41:181-6.

61. Shen WW. The metabolism of atypical antipsychotic drugs: an update. *Ann Clin Psychiatry* 1999;11:145-58.

62. Bergemann N, Frick A, Parzer P, Kopitz J. Olanzapine plasma concentration, average daily dose, and interaction with co-medication in schizophrenic patients. *Pharmacopsychiatry* 2004;37:63-8.

63. Gex-Fabry M, Balant-Gorgia AE, Balant LP. Therapeutic drug monitoring of olanzapine: the combined effect of age, gender, smoking, and comedication. *Ther Drug Monit* 2003;25:46-53.

64. Kapur S, Roy P, Daskalakis J, Remington G, Zipursky R. Increased dopamine D2 receptor occupancy and elevated prolactin level associated with addition of haloperidol to clozapine. *Am J Psychiatry* 2001;158:311-4.

65. Matthiasson P, Erlandsson K, Costa DC, Waddington W, Visvikis D, Collum I, et al. Amisulpride augmentation of clozapine and striatal dopamine d2 receptor binding potential. A 123-I-IBZM study. *Schizophr Res* 2002;53(3 Suppl 1):208-9.