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ORIGINAL PAPER

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Risperidone augmentation of clozapine

A critical review

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Abstract *Objective* Atypical antipsychotics are frequently used as augmentation agents in clozapine-resistant schizophrenic patients. Risperidone (RIS) is the one most studied as a clozapine (CLZ) adjunct. The aim of this study is to critically review all published studies regarding the efficacy and safety of RIS as an adjunctive agent in CLZ-resistant schizophrenic or schizoaffective patients. *Methods* A MEDLINE search from January 1988 to June 2005 was conducted. Identified papers were examined against several clinical, pharmacological and methodological parameters. *Results* A total of 15 studies were found (2 randomized controlled trials, 3 open-label trials (OTs) and 8 case-studies (CSs)) comprising 86 schizophrenic or schizoaffective patients (mean age 38.4 years). Mean CLZ dosage during the combined treatment was 474.2 mg/day. Plasma CLZ levels were assessed in 62 patients (72.1%). RIS was added at a mean dosage of 4.6 mg/day for a mean of 7.9 weeks. Significant improvement in psychopathology was reported for 37 patients (43%). A lower RIS dosage and a longer duration of the trial seemed to be associated with a better outcome. Main side effects reported were: extrapyramidal symptoms or akathisia (9.3%), sedation (7%) and hypersalivation (5.8%). *Conclusions* Existing evidence encourages the use of RIS as an adjunctive agent in CLZ-resistant schizophrenic or schizoaffective patients.

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Introduction

Approximately 40–70% of treatment-resistant schizophrenic patients are also clozapine-resistant as they fail to respond to clozapine (CLZ) monotherapy or are partial responders [17, 25]. During the last years several adjunctive agents have come into clinical practice to enhance the antipsychotic efficacy of CLZ [5, 7]. For most of them evidence is confounding and comes mainly from case-studies or open-label trials (OTs) as randomized controlled trials are still sparse [19]. Augmentation with other atypical antipsychotics is one of the most frequently used treatment options in CLZ-resistant patients [12, 35]. Risperidone (RIS), the first novel atypical antipsychotic that came into clinical practice, seems to be the one most studied as a CLZ adjunct.

The purpose of this study is to pool and critically review all published studies regarding the efficacy and safety of RIS as an augmentation agent in CLZ-resistant schizophrenic or schizoaffective patients.

Method

A MEDLINE search for all studies published from January 1988 to June 2005 assessing the efficacy and safety of RIS as an adjunctive agent in CLZ-resistant schizophrenic or schizoaffective patients was conducted using the keywords of 'clozapine', 'resistant', 'refractory', 'schizophrenia', 'risperidone', 'augmentation' and 'adjunctive'. In addition, the reference sections of the identified papers and main reviews [5, 7, 12, 35] were screened. Studies with no efficacy reports were excluded from our review. Furthermore, patients who were not treated with CLZ in monotherapy before an augmentation regimen were excluded from our analysis.

All the included papers were critically reviewed and examined against the following set of parameters: clinical and demographic characteristics of patients, dosage and duration of CLZ mono-

therapy, prior RIS monotherapy trials, baseline severity of psychopathology, CLZ dosage during the combined treatment, RISP dosage, other psychotropic medications concurrently used, plasma CLZ levels assessed, duration of the trial and follow-up, clinical outcome, outcome measures used and side effects reported.

Results

Several studies with no efficacy reports focusing on CLZ–RIS pharmacokinetic interactions [30], adverse effects associated with the combination [3, 9, 13, 15, 20, 33] or other effects [29] were not included in our review. Our search finally resulted in 2 randomized, double-blind, placebo-controlled trials (RCTs) [2, 16], 3 open-label trials (OTs) [11, 14, 36] and 8 case-studies (CSs) [1, 8, 21, 24, 26, 31, 32, 37], comprising a total of 121 patients. Out of 70 patients included in the two RCTs, only 36 patients received a CLZ–RIS combination while the rest received a CLZ–placebo (PBO) combination and they were excluded from our analysis. Besides, for one out of three patients included in one CS CLZ had not been tried in monotherapy before augmenting an ineffective RIS regimen [32]. This patient was also excluded from our analysis. Data of 86 schizophrenic or schizoaffective patients were finally analyzed.

Table 1 shows data from two RCTs including a total of 36 schizophrenic or schizoaffective patients on CLZ–RIS combination and from three OTs including a total of 37 patients (34 schizophrenic and 3 schizoaffective). RIS was more efficacious as a CLZ adjunct than PBO only in one RCT [16] and significant improvement in patients' psychopathology was reported in two OTs [14, 36].

Both RCTs included inpatients as well as outpatients. Inpatients were included in two OTs [11, 36], while outpatients in the third [14]. Patients' sex distribution was not reported in one trial [36], while in the rest a total of 44 males and 16 females were included. It is worth noting that in the positive-outcome RCT [16] the study population consisted mostly of males (95%). Patients in all trials had comparable mean ages ranging from 35.3 to 41.7 years. Duration of illness was not reported in two OTs [11, 14].

The duration of prior CLZ monotherapy was shorter than 12 weeks in only two OT patients [36]. It was not exactly reported in two OTs [11, 14], while in the remaining trials the mean duration of CLZ monotherapy varied highly from 22 to 396.9 weeks. CLZ monotherapy dosage was reported in detail in only one RCT [2] and one OT [36]. No RCT patient had been on a CLZ monotherapy dosage lower than 300 mg/day. About 21 out of 70 RCT patients and 9 patients in 1 OT [36] had failed to respond or had responded poorly to prior RIS monotherapy, while relevant information was missing in the remaining two OTs.

Clozapine dosage during the trial was not reported in one OT [11]. The mean CLZ dosage during the combined treatment was comparable among all the remaining trials, except one OT in which it was significantly lower [36]. The mean RIS dosage ranged from 3 to 5.3 mg/day. The lowest mean RIS dosages were recorded in the positive-outcome trials (mean RIS dosage: 3.7 mg/day for positive-outcome trials vs. 5.2 mg/day for negative-outcome trials). Plasma CLZ levels were assessed in both RCTs but reported in detail in none. They were also assessed in the majority (22 out of 24) of the patients of two OTs [11, 14]. In all trials, levels remained unchanged after RIS was added to CLZ.

One RCT had a 12–week duration [16] while the other had a 6-week duration [2]. Two OTs had a 4-week duration [11, 14] while in the third RIS augmentation was maintained for a mean of 12 weeks (range 4–28 weeks) [36]. The positive-outcome trials had the longest durations reported (mean duration of trial: 9.3 weeks for positive-outcome trials vs. 5 weeks for negative-outcome trials). Primary outcome measures used were the Brief Psychiatric Rating Scale (BPRS) [14, 16] and the Positive And Negative Syndrome Scale (PANSS) [2, 11, 36]. A total of 9 RCT patients (25% of all CLZ + RIS patients in the two RCTs) and 17 OT patients (45.9% of all OT patients) had a 20% or greater decrease in psychopathology, as measured with BPRS or PANSS.

Side effects reported in the two RCTs included: akathisia (2 patients), extrapyramidal symptoms (1 patient), sedation (5 patients) and serum prolactin elevation. Side effects reported in the three OTs included: hypersalivation (5 patients), mild akathisia (4 patients), exacerbation of compulsive behaviours-rubbing (one patient), orthostatic hypotension (one patient) and fatigue (one patient). Only two patients dropped out [2, 11] (one because of orthostatic hypotension [11]).

Table 2 shows data from eight CSs including a total of 13 patients (11 schizophrenic and 2 schizoaffective, 10 males and 3 females). Patients in the CS group had a mean age of 35.8 (± 11.2) years (range 18–60 years). Duration of illness was not reported for only one CS patient and in the rest it ranged from 2.5 to 31 years (mean 13.9 ± 8.2 years).

The duration of CLZ monotherapy was not reported for two CS patients [24] while in the rest it ranged from 5 to 520 weeks (mean 96.4 ± 145.1 weeks). It was shorter than 12 weeks in two CS patients [31]. CLZ dosage during monotherapy ranged between 250 and 900 mg/day (mean 609.6 ± 185.4 mg/day). It was above 300 mg/day in 12 patients (92.3% of all CS patients). Five patients in three CSs [24, 26, 31] had failed to respond or had responded poorly to prior RIS monotherapy.

Clozapine dosage during the combined treatment ranged from 150 to 900 mg/day (mean 492.3 ± 222.6 mg/day). RIS dosage varied from 1 to 10 mg/day (mean 5.8 ± 2.3 mg/day). Other psychotropic medications were concurrently used in two patients [24]. Plasma CLZ levels were assessed in only

Table 1 Risperidone augmentation randomized placebo-controlled trials (RCT) and open-label trials (OT) in clozapine-resistant schizophrenic or schizoaffective patients

Authors–type of trial	Patients' number, diagnosis	Sex, age, duration of illness (years)	Duration of CLZ monotherapy (weeks)	CLZ monotherapy dosage (mg/day)	CLZ dosage during the trial (mg/day)	RIS dosage (mg/day)	Plasma CLZ levels (ng/ml)	Duration of trial (weeks)	Baseline psychopathology–Outcome	Side effects
Josiassen et al. [16]–RCT	CLZ ± RIS 20 sch/saf [CLZ ± PBO 20 sch/saf]	CLZ ± RIS 19 m/1 f, 40.8 ± 6.9, 21.8 ± 7.0	Overall 396.9 ± 174.4 (30–584) (9 pts*)	≥600 (or plasma ≥350 ng/ml)	CLZ ± RIS 528.8 ± 166.7	4.43 ± 1.5 (week 12) (2 pts#)	ns change	12	Positive (CLZ ± RIS Baseline BPRS tot 48.8 ± 9.2, BPRS tot ↓ by ≥20%: 7 pts)	RIS > PBO in ↓ SAS, weight ns, CLZ ± RIS akathisia (2 pts)
Anil Yagcioglu et al. [2]–RCT	CLZ ± RIS 16/15[a] sch/saf [CLZ ± PBO 14 sch/saf]	CLZ ± RIS 9 m/7 f, 35.3 ± 10.8, 14.4 ± 9.1	Overall 127.6 ± 116.8 (12 pts*) CLZ ± RIS 106.8 ± 114.8	300–900	CLZ ± RIS 515.6 ± 138.7	5.1 ± 1.3 (week 6) (6 pts#)	ns change	6	Negative (CLZ ± RIS Baseline PANSS tot 77.4 ± 1.65, PANSS tot ↓ by ≥20%: 2 pts)	SAS, BAS, AIMS ns, weight ns CLZ ± RIS sedation (5 pts), EPS (1 pt), prolactin ↑
Henderson & Goff [14]–OT	10 sch, 2 saf	7 m, 5 f 38.7 ± 4.5, NR	≥52	Optimal or maximum tolerated, (2 pts#)	250–700 (479 ± 121)	2–6 (3.8 ± 1.4)	Monotherapy: 483.3 ± 195.6 (132–777), (10 pts >350) Combination (7 pts): ↑ ns	4	Positive (Baseline BPRS tot 42.2 ± 5.0, BPRS tot, pos ↓ by ≥20% :10 pts, BPRS neg ↓ by ≥20% :7 pts, BPRS dep ↓ by 20% :5 pts]	Mild akathisia (4 pts), hypersalivation (5pts), fatigue (1 pt)
Taylor et al. [36]–OT	12 sch, 1 saf	Sex NR, mean 38, mean 18	4–45 (mean 22) [2 pts <12] (9 pts*)	200–800 (487 ± 179)	150–450 (mean 317)	2–6 (3.0 ± 1.2)	NR	4–28 (mean 12)	Positive (Baseline PANSS tot >95, PANSS tot ↓ by ≥20% :7 pts, CGI-I: marked 4 pts, minimal 6 pts, none 3 pts)	Compulsive rubbing (1 f pt)
de Groot et al. [11]–OT	12/11[a] sch	9 m, 3 f 41.7 ± 10.7, NR	≥26	Therapeutic plasma CLZ levels	NR	1–6 (5.3 ± 1.4)	(10 pts) Monotherapy: 377.2 ± 129.0, Combination: 355.1 ± 97.0 (ns change)	4	Negative (Baseline PANSStot 81.6 ± 12.9, PANSS tot, pos, neg ↓ by ≥20% :0 pts)	Orthostatic hypotension (1 pt–dropped out)

sch = schizophrenic, saf = schizoaffective, m = male, f = female, CLZ = clozapine, RIS = risperidone, PBO = placebo, NR = not reported, pt(s) = patient(s), ↑ = increase, ↓ = decrease, ns = non-significant, BPRS = Brief Psychiatric Rating Scale, PANSS = Positive And Negative Syndrome Scale, tot = total, pos = positive, neg = negative, dep = depression, CGI-I = Clinical Global Impression- Improvement Scale, SAS = Simpson–Angus Rating Scale for Extrapyramidal Side Effects, BAS = Barnes Akathisia Scale, AIMS = Abnormal Involuntary Movements Scale, EPS = extrapyramidal symptoms

* Patients had failed to respond or had responded poorly to risperidone monotherapy

Dosage was limited by side effects

[a] Intention-to-treat group (completer group)

Table 2 Risperidone augmentation case-studies (CS) in clozapine-resistant schizophrenic or schizoaffective patients

Authors	Patients' number, diagnosis	Sex, age, duration of illness (years)	Duration of CLZ monotherapy (weeks)	CLZ monotherapy dosage (mg/day)	CLZ dosage in combined treatment (mg/day)	RIS dosage (mg/day)	Plasma CLZ levels (ng/ml)	Duration of trial/ follow-up	Outcome	Side effects
McCarthy & Terkelsen [24]	1 saf	m, 29, 4	NR*	400	150**	6	NR	3 w/6 mo	Positive (clinical improvement)	Sedation (1 pt)
	1 sch	m, 38, 20	NR	750 → 250#	200**	6	NR	2 w/7 mo		
Tyson et al. [37]	1 saf	m, 32, 10	≥20	600	600	2	344 → 598	2 w/NR	Positive (clinical improvement)	Transient lightheaded-ness
Morera et al. [26]	1 sch	m, 34, 14	52*	500	300	6	NR	12 w/24 mo	Positive [BPRS ↓ 20 → 11/22 → 12]	None
	1 sch	m, 54, 31	26*	600	400	6	NR	6 w/NR		
Raskin et al. [32]	1 sch	f, 60, NR	520	700	550	2	NR	5 w/NR	Positive [PANSS total ↓ by 30%/25%, PANSS positive ↓ by 46%/32%]	NR
	1 sch (out of 3 [a])	m, 36, 20	208	900	600	6	NR	16 w/NR		
Adesanya & Pantelis [1]	1 sch	m, 41, 17	52	600	600	6	646	6 w/NR	Positive (clinical improvement)	NR
	1 sch	m, 39, 21	>52	900	900	6	452 Monotherapy	12 w/6 mo		
Raju et al. [31]	1 sch	m, 26, 6	5*	800	800	10	NR	8 w/7 mo	Positive [PANSS total ↓ 41 → 32/84 → 47]	none
	1 sch	m, 18, 2.5	6*	800 → 400#	600	10	NR	4 w/3 mo		
Koreen et al. [21]	1 sch	f, 22, 5	104	675	500	4	829 → 1800 → 1100	1 w/NR	Negative (no clinical improvement)	Mild oculogyric crises
Chong et al. [8]	1 sch	f, 36, 16	>14	600	200	6	NR	16 w/NR	Negative (no clinical improvement)	Compulsive symptoms (hoarding)↑

sch = schizophrenic, saf = schizoaffective, m = male, f = female, mo = months, w = weeks, NR = not reported, ↑ = increase, ↓ = decrease, pt(s) = patient(s), CLZ = clozapine, RIS = risperidone, BPRS = Brief Psychiatric Rating Scale, PANSS = Positive And Negative Syndrome Scale

* Patients had failed to respond or had responded poorly to risperidone monotherapy

** Other psychotropic medications were concurrently used (lithium/ fluoxetine)

Dosage was limited by side effects

[a] The third patient had not been previously treated with clozapine. Clozapine was added to a risperidone regimen

four CS patients [1, 21, 37]. In two of them plasma levels were found markedly elevated 1 week [21] and 2 weeks [37] after the addition of RIS.

Outcomes in the CS group were reported after a period varying from 1 [21] to 16 weeks [8, 32] (mean 7.15 ± 5.24 weeks). However, this period was 12 weeks or longer only in four CS patients. Six patients included in four CSs [1, 24, 26, 31] were followed-up for a period ranging from 3 to 24 months (mean 8.83 ± 7.57 months) post-discharge. Outcome measures were used for only six patients in three CSs and included BPRS [26] and PANSS [31, 32]. In the remaining CSs outcome was judged by subjective clinical impression. The combined treatment was effective in 11 patients included in six CSs (84.6% of all CS patients) [1, 24, 26, 31, 32, 37].

Side effects reported in the eight CSs included: exacerbation of compulsive behaviours-hoarding (one patient), sedation (one patient), mild oculogyric crises (one patient) and transient lightheadedness (one patient).

Discussion

We reviewed data of 86 CLZ-resistant schizophrenic or schizoaffective patients included in 2 randomized controlled trials, 3 OTs and 8 CSs who were treated with combined CLZ–RIS therapy. A major limitation of the study was that individual data from patients included in the RCTs and OTs were not available. Therefore, we were not able to pool and statistically analyze patients' data and predictors of outcome could not be isolated. Moreover, the use of different scales (BPRS or PANSS) did not allow head-to-head comparisons of baseline psychopathology between trials.

On the whole male schizophrenic patients prevailed in the population analyzed. The patients had a mean age of 38.4 years. Mean CLZ dosage during the combined treatment was 474.2 mg/day (for 74 patients it was reported for) and mean RIS dosage was 4.6 mg/day. The duration of the combined treatment ranged widely from 1 to 28 weeks (mean 7.9 weeks). Outcome measures were used in 79 patients in total (91.9%). On the whole, RIS was effective in augmenting response to CLZ in 37 patients (43%). Although predictors of outcome could not be isolated a lower RIS dosage and a longer duration of the trial seemed to be associated with a better outcome. The most frequently reported side effects were: extrapyramidal symptoms or akathisia (9.3%), sedation (7%) and hypersalivation (5.8%).

It was of principal concern in this review to check whether patients included met operational criteria for CLZ-resistance. Although the time and dose parameters for an adequate CLZ trial remain controversial most authors agree on a minimum of 12 weeks and 300 mg/day, respectively [4, 10]. Furthermore, optimal clinical response has been associated with plasma CLZ levels greater than 350–420 ng/ml [22, 23, 28]. Our analysis showed that CLZ monotherapy was maintained long enough (for at least 12 weeks) in 80 patients in total (93%). Moreover, CLZ monotherapy dosage was adequate (above 300 mg/day) in all RCT patients, in 92.3% of all CS patients while detailed information about the OT group is missing. Besides, plasma CLZ levels were performed in 62 patients in total (72.1%). Therefore, at least some patients studied might not be truly CLZ-resistant, since they may not have been offered an adequate CLZ monotherapy trial.

Our analysis also places emphasis on other methodological shortcomings of studies analyzed: incomplete demographic and clinical data of patients, especially in the OT group; lack of outcome measures and concurrent use of other psychotropic medications in the CS group. A final point is also noteworthy. According to Freudenreich and Goff [12], the safest method to draw conclusions about the efficacy of a combination of antipsychotics warrants each of them being previously tried in optimal monotherapy. Therefore, a CLZ + RIS combination should be tested after both CLZ and RIS have failed in monotherapy. However, prior RIS monotherapy trials have been reported in only 35 patients.

The mechanism underlying CLZ–RIS synergistic antipsychotic effect is unknown. Both pharmacodynamic and pharmacokinetic interactions have been implicated. RIS's higher affinity for D2 receptors compared to CLZ might contribute to an additive effect on low D2 receptor occupancy already achieved by CLZ. Optimizing D2 receptor occupancy may be necessary for maximal response to antipsychotics at least in a group of schizophrenic patients [18, 27]. Pharmacokinetic interactions may also contribute to the improved antipsychotic efficacy of the combined regimen although they might also be responsible for serious side effects [3, 9, 13, 15, 20, 33]. Existing evidence mitigates the importance of CLZ–RIS pharmacokinetic interactions: CLZ levels were markedly elevated in 2 cases [21, 37] but remained unchanged in 4 trials [2, 11, 14, 16] and a recent pharmacokinetic study [30]. RIS and CLZ are both partially metabolized by the hepatic microsomal cytochrome P450 2D6. However, CLZ is mainly metabolized through other cytochrome enzymes (P450 1A2, 3A4) [6, 34].

In conclusion, existing evidence encourages the use of RIS as an adjunctive agent in at least a group of CLZ-resistant schizophrenic or schizoaffective patients. However, the methodological discrepancies and shortcomings of analyzed studies limit the impact of evidence provided. Further carefully-conducted controlled trials are needed to establish RIS augmentation as a widely accepted treatment option in this demanding group of patients.

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