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In Review

Antipsychotic Polypharmacy and Corrected QT Interval: A Systematic Review

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Objective: It remains unclear whether antipsychotic polypharmacy, a common clinical practice, is related to an increased risk of corrected time between start of Q wave and end of T wave (QTc) interval prolongation. We conducted a systematic review of the literature to address this important issue.

Method: A systematic literature search was conducted in October 2014, using MEDLINE, Embase, and PsycINFO. Studies and case reports were included if they reported QTc intervals or QTc interval changes before and after antipsychotic polypharmacy or QTc intervals in both antipsychotic polypharmacy and monotherapy groups.

Results: A total of 21 articles (10 clinical trials, 4 observational studies, and 7 case reports) met inclusion criteria. The clinical trials have shown that a combination treatment with risperidone or pimozide is not obviously related to an increase in QTc interval, whereas ziprasidone or sertindole combined with clozapine may prolong QTc interval. Among the 4 observational studies, antipsychotic polypharmacy was not clearly associated with QTc prolongation in 3 studies, each cross-sectional. In contrast, one prospective study showed a significant increase in QTc interval following antipsychotic coadministration. The case reports indicated an increased risk of QTc prolongation in at least some patients receiving antipsychotic polypharmacy.

Conclusions: Currently available evidence fails to confirm that antipsychotic polypharmacy worsens QTc prolongation in general, although the evidence is scarce and inconsistent. Clinicians are advised to remain conservative in resorting to antipsychotic polypharmacy, as a combination of some QTc-prolongation liable antipsychotics may further prolong QTc interval, and efficacy supporting the clinical benefits of antipsychotic polypharmacy is equivocal, at best.

Polypharmacie antipsychotique et intervalle QT corrigé : une revue systématique

Objectif : Il reste à déterminer si la polypharmacie antipsychotique, une pratique clinique courante, est liée à un risque accru de temps corrigé dans l'allongement de l'intervalle entre le début de l'onde Q et la fin de l'onde T (QTc). Nous avons mené une revue systématique de la littérature pour aborder ce problème important.

Méthode : Une recherche systématique de la littérature a été menée en octobre 2014, dans les bases de données MEDLINE, Embase et PsycINFO. Les études et les études de cas étaient incluses si elles rendaient compte d'intervalles QTc ou de changements d'intervalles QTc avant et après la polypharmacie antipsychotique ou d'intervalles QTc dans les groupes de polypharmacie antipsychotique et de monothérapie.

Résultats : Un total de 21 articles (10 essais cliniques, 4 études par observation, et 7 études de cas) satisfaisaient aux critères d'inclusion. Les essais cliniques ont montré qu'un traitement combiné par rispéridone ou pimozide n'est pas clairement lié à une

augmentation de l'intervalle QTc, alors que la ziprasidone ou le sertindole combiné à la clozapine peuvent prolonger l'intervalle QTc. Dans les 4 études par observation, la polypharmacie antipsychotique n'était pas clairement associée à l'allongement du QTc dans 3 études, toutes transversales. Par contre, une étude prospective montrait une augmentation significative de l'intervalle QTc suivant une co-administration antipsychotique. Les études de cas indiquaient un risque accru d'allongement du QTc chez au moins certains patients recevant une polypharmacie antipsychotique.

Conclusions : Les données probantes actuellement disponibles ne confirment pas que la polypharmacie antipsychotique aggrave l'allongement du QTc en général, car les données probantes sont rares et non consistantes. Il est recommandé que les cliniciens demeurent prudents lorsqu'ils ont recours à la polypharmacie antipsychotique, étant donné qu'une combinaison de certains antipsychotiques est susceptible de prolonger davantage l'intervalle QTc, et que l'efficacité à l'appui des avantages cliniques de la polypharmacie antipsychotique est au mieux équivoque.

Most typical and atypical antipsychotics have a potential to prolong the QTc interval (that is, QTc-prolonging drugs),[1–3] at least in part by inhibiting the hERG- (also known as *KCNH2*) encoded potassium channels.[4,5] The QT interval is the time between the beginning of the Q wave and the end of the T wave on the electrocardiogram, representing ventricular repolarization. Because QT interval shortens with increasing heart rate, it is usually corrected for heart rate (that is, QTc interval), with the 2 main formulae: Bazett's formula ($QTcBZT = QT/RR^{1/2}$), which is most widely used, and Fridericia's formula ($QTcFRD = QT/RR^{1/3}$). The QTcBZT is less accurate than the QTcFRD when a heart rate is altered, as it over-corrects at an elevated heart rate and under-corrects at a heart rate below 60 beats per minute.[6] QTc interval prolongation is considered a risk factor in fatal polymorphic ventricular tachycardia, namely, TdP,[7] which can result in sudden cardiac death. In fact, prolonged QTc interval is related to an increased risk of total, cardiovascular, coronary, and sudden cardiac death,[8] which is in line with the observation that use of hERG channel blockers is associated with a risk of sudden cardiac death in the general population.[9]

While the risk of QTc prolongation caused by each individual antipsychotic has been the focus of extensive research, potential additive or synergistic effects of antipsychotic polypharmacy (that is, 2 or more antipsychotics concurrently prescribed) on QTc interval have rarely been reported in the literature, to date. This issue, critically important from a safety perspective, is particularly pertinent in light of the widespread use of antipsychotic polypharmacy; prevalence rates range from 12.9% to 35.0%,[10] despite equivocal efficacy of antipsychotic combinations.[11–13] To address this clinically relevant question, we conducted a systematic review of the literature on antipsychotic polypharmacy and QTc interval.

Clinical Implications

- Existing evidence regarding antipsychotic polypharmacy and QTc interval is scarce and inconsistent.
- Currently available evidence fails to confirm that antipsychotic polypharmacy worsens QTc prolongation in general.
- A combination of some high-risk, QTc-prolonging antipsychotics may prolong QTc interval.

Limitations

- The literature search was limited to the English language.
- Most of the articles depend on Bazett's formula rather than Fridericia's or other formulae in calculating QTc intervals.
- Too few data are available to evaluate possible additive or synergistic effects of specific antipsychotic combinations on QTc interval.

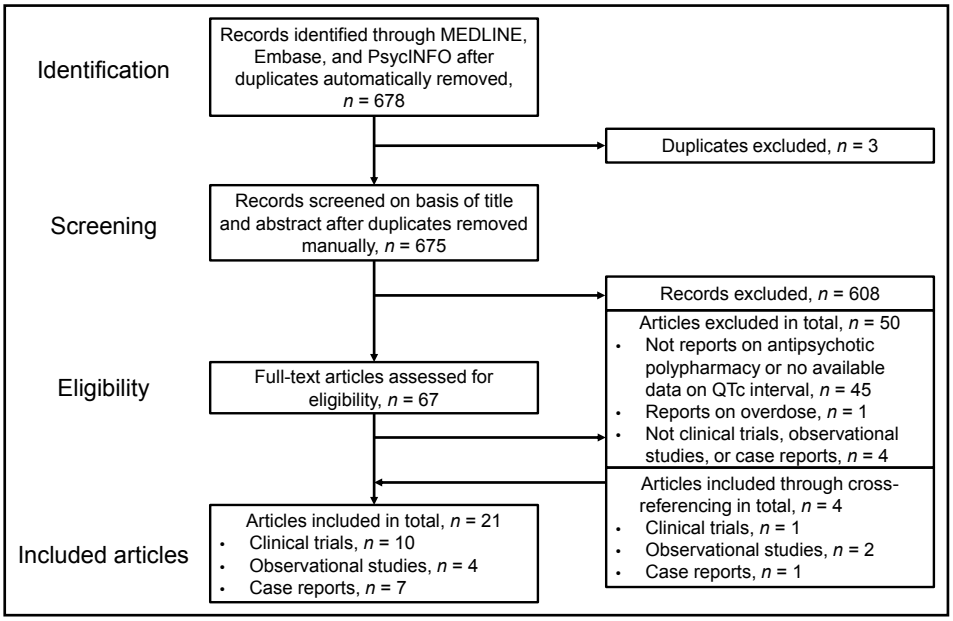
Abbreviations

hERG	human *ether-à-go-go*-related gene
LAI	long-acting injectable
QT	time between start of Q wave and end of T wave
QTc	corrected QT
QTcBZT	QTc calculated with Bazett's formula
QTcFRD	QTc calculated with Fridericia's formula
RCT	randomized controlled trial
RR	time between 2 consecutive R waves
TdP	torsade de pointes

Method

A systematic literature search was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) Statement,[14] using MEDLINE (1946–present), Embase (1947–present), and PsycINFO (1806–present) on October 15, 2014. The following key words were used: (qt OR qtc) AND antipsychotic* AND (combin* OR polypharmacy OR polytherapy OR augment* OR adjunct* OR adjuvant* OR add* OR concomitant* OR concurrent* OR comedication* OR cotreatment* OR coadministrat* OR enhance* OR simultaneous* OR supplement*) NOT (addict* OR address*). The key words related to antipsychotic polypharmacy were determined in reference to the search terms used in a previous meta-analysis comparing antipsychotic polypharmacy with monotherapy,[15] with some modifications. The literature

Figure 1 PRISMA flow diagram of the literature search



QTc = corrected time between start of Q wave and end of T wave

search was limited to the English language, and a cross-referencing of the identified references was also conducted.

Clinical trials (that is, intervention studies), observational studies, and case reports that met the following 2 criteria were included in this review: reports in which 2 or more antipsychotics were concurrently used; and reports in which QTc intervals or QTc interval changes before and after antipsychotic polypharmacy were recorded, or reports in which QTc intervals in antipsychotic polypharmacy and monotherapy groups were compared. As our focus was on antipsychotic polypharmacy and QTc intervals within usual clinical circumstances, studies on antipsychotic overdose were excluded.

The following information was collected from the reports included in the present review: study design (only for clinical trials and observational studies); study duration (only for clinical trials and prospective observational studies); the number of patients (only for clinical trials and observational studies); each patient's diagnosis, age, and sex; QTc intervals or QTc interval changes before and after antipsychotic polypharmacy or QTc intervals in both antipsychotic polypharmacy and monotherapy groups; and, types and doses of antipsychotics (if available).

Results

A total of 21 articles (10 clinical trials,[16–25] 4 observational studies,[26–29] and 7 case reports[30–36]) were identified through our literature search (Figure 1). QTc interval was the primary focus reported in 9 of these articles (all 4 observational studies[26–29] and 5 case reports[30–33,36]).

Clinical Trials

Among the clinical trials,[16–25] 8 were RCTs[16,18,19,21–25] and the remaining 2 were single-arm, prospective trials.[17,20] Seven RCTs compared a combination of 2 antipsychotics with 1 of the 2 antipsychotics (plus placebo),[16,18,21–25] while 1 RCT compared 2 different types of antipsychotic polypharmacy.[19] All patients were diagnosed with schizophrenia or schizoaffective disorder. All but 1 trial examined augmentation of clozapine with another antipsychotic (note: in 1 study,[20] clozapine or olanzapine plus another antipsychotic was examined).[16–20,22–25] The results of QTc intervals at baseline and at end point, or changes in QTc interval from baseline to end point, are summarized in Table 1.

Risperidone was examined in 3 trials,[16,19,21] with all showing that combination treatment with risperidone did not significantly increase QTc interval. Two RCTs found no significant difference between clozapine plus risperidone and clozapine plus placebo,[16] or risperidone plus haloperidol and risperidone alone, although the dose of risperidone in the former was one-half of that in the latter (2 and 4 mg/day).[21] One RCT, comparing clozapine plus risperidone with clozapine plus ziprasidone, indicated that QTc changes were not significant in the clozapine plus risperidone group.[19] Ziprasidone was tested in 4 trials.[17,19,20,25] One RCT showed that clozapine plus ziprasidone significantly prolonged QTc interval, compared with clozapine plus risperdione; however, there was no monotherapy arm in this study.[19] Conversely, no significant difference in QTc intervals was observed between clozapine plus ziprasidone and clozapine alone in the other RCT.[25] Similarly, 2 single-arm trials[17,20] found that ziprasidone augmentation of clozapine did not significantly increase QTc interval. Aripiprazole was investigated in one trial,[18] revealing no significant difference in QTc changes between clozapine plus aripiprazole and clozapine plus placebo. Sertindole was examined in one study[23]; sertindole plus clozapine

Table 1 Clinical trials on antipsychotic polypharmacy and corrected QT (QTc) interval

					Antipsychotic polypharmacy				Antipsychotic monotherapy				
Study	Year	Design	Diag-nosis	Duration	Anti-psychotics (mean dose, mg/day)	*n* (male; female)	Mean age, years	Mean QTc baseline to end point difference, ms (within-group difference)	Anti-psychotics (mean dose, mg/day)	*n* (male; female)	Mean age, years	Mean QTc baseline to end point difference, ms (within-group difference)	Group differ-ence
Anil Yağcioğlu et al[16]	2005	DB-RCT	Sz and SAD	6 weeks	CLZ (516) + RIS (6)	16 (9; 7)	35.3	441 to 430 (n/a)	CLZ (414) + PLB	14 (11; 3)	31.2	437 to 450 (n/a)	ns
Ziegenbein et al[17]	2005	OL	Sz	6 months	CLZ (570) + ZIP (147)	9 (5; 4)	37.3	n/a	n/a	n/a	n/a	n/a	n/a
Chang et al[18]	2008	DB-RCT	Sz	8 weeks	CLZ (304) + APZ (15.5)	29 (22; 7)	33.2	439 to 443 (ns)	CLZ (291) + PLB	32 (26; 6)	31.7	440 to 441 (ns)	ns
Zink et al[19]	2009	OL-RCT	Sz and SAD	6 weeks	CLZ (361) + ZIP (134)	12 (7; 5)	31.8	388[c] to 403[c] (s)	n/a	n/a	n/a	n/a	s
					CLZ (407) + RIS (3.8)	12 (7; 5)	37.3	391[c] to 381[c] (ns)	n/a	n/a	n/a	n/a	
Henderson et al[20]	2009	OL	Sz and SAD	6 weeks	CLZ (n/a) or OLZ (n/a) + ZIP (160)	21 (17; 4)	49	417 to 420 (ns)	n/a	n/a	n/a	n/a	n/a
Lin et al[21]	2010	DB-RCT	Sz	6 weeks	RIS (2) + HPD (2)	46[a] (n/a; n/a)	38[b]	410 to 407 (n/a)	RIS (4)	42[a] (n/a; n/a)	38[b]	413 to 405 (n/a)	ns
Friedman et al[22]	2011	DB-RCT	Sz and SAD	12 weeks	CLZ (519) + PMZ (6.5)	25 (21; 4)	45.5	+9.0 (n/a)	CLZ (478) + PLB	28 (20; 8)	44.4	–1.5 (n/a)	ns
Nielsen et al[23]	2012	DB-RCT	Sz	12 weeks	CLZ (394) + SER (16)	25 (15; 10)	41.8	440 to 452 and 405[c] to 412[c] (n/a and ns)	CLZ (435) + PLB	25 (15; 10)	42.7	450 to 450 and 409[c] to 420[c] (n/a and n/a)	s and ns
Gunduz-Bruce et al[24]	2013	DB-RCT	Sz and SAD	12 weeks	CLZ (n/a) + PMZ (4)	14 (10; 4)	44.3	412 to 420 (n/a)	CLZ (n/a) + PLB	14 (10; 4)	41.5	409 to 413 (n/a)	ns
Muscatello et al[25]	2014	DB-RCT	Sz	16 weeks	CLZ (429) + ZIP (80)	20 (5; 15)	36.5	403 to 408 (s)	CLZ (463) + PLB	20 (8; 12)	33.5	408 to 405 (n/a)	ns

[a] QTc intervals were measured in 29 patients.

[b] For whole patients

[c] Calculated with Fridericia's formula

CLZ = clozapine; DB = double-blind; HPD = haloperidol; n/a = not available or not applicable; ns = nonsignificant; OL = open-label; PLB = placebo; PMZ = pimozide; RCT = randomized controlled trial; RIS = risperidone; s = significant; SAD = schizoaffective disorder; SER = sertindole; Sz = schizophrenia; ZIP = ziprasidone

Table 2 Observational studies on antipsychotic polypharmacy and corrected QT (QTc) interval

				Antipsychotic polypharmacy			Antipsychotic monotherapy			
Study	Year	Design	Diagnosis	*n* (male; female)	Mean age, years	Mean QTc, ms at mg/day	*n* (male; female)	Mean age, years	Mean QTc, ms at mg/day	Group difference
Mackin and Young[26]	2005	Cross-sectional	n/a	12 (n/a; n/a)	45.3[a]	403	53 (n/a; n/a)	45.3[a]	416	ns
Correll et al[27]	2009	Cross-sectional	n/a	38 (25; 13)	40.9	403 at 525[b,c]	73 (44; 29)	44.5	408 at 245[b,c]	ns
Ramos-Ríos et al[28]	2010	Cross-sectional	Sz	137 (n/a; n/a)	55.8[a]	n/a	34 (n/a; n/a)	55.8[a]	n/a	ns[d]
Di Sciascio et al[29]	2011	Prospective	Sz and BD	42 (30; 12)	36.0	369 at 477[b] to 387 at 845[b] s	33 (25; 8)	39.2	365 at 398[b] to 363 at 449[b] ns	n/a

[a] For whole patients

[b] Mean chlorpromazine-equivalent dose

[c] All patients were treated with atypical antipsychotics

[d] The number of antipsychotics did not significantly predict QTc interval.

BD = bipolar disorder; n/a = not available or not applicable; ns = nonsignificant; s = significant; Sz = schizophrenia

significantly increased QTcBZT interval, compared with clozapine alone, which was not the case with QTcFRD interval. Pimozide was examined in 2 studies,[22,24] with both investigations demonstrating no significant effect of pimozide plus clozapine on QTc prolongation, compared with clozapine monotherapy.

Observational Studies

Four observational studies[26–29] (3 cross-sectional studies[26–28] and 1 prospective study[29]) were identified (Table 2). All 3 cross-sectional studies[26–28] failed to demonstrate any significant effect of antipsychotic polypharmacy on the QTc interval: 2 studies[26,27] compared QTc intervals between antipsychotic polypharmacy and monotherapy, failing to show any significant differences between the 2 groups; another study[28] found that QTc interval was not significantly influenced by dose, class, or number of antipsychotics. In contrast to these cross-sectional studies, one prospective study[29] indicated that a significant increase in QTc interval was found in patients who received another antipsychotic in addition to an ongoing antipsychotic (that is, monotherapy to polypharmacy), while no significant change in QTc interval was observed in patients who had their antipsychotics switched to another (that is, monotherapy to a different type of monotherapy).

Case Reports

A total of 11 cases in 7 case reports[30–36] were identified (Table 3). In 2 cases,[30,31] QTc prolongations were improved after transitioning 2 antipsychotics to 1 single, different antipsychotic; of note, this improvement could have been due to a difference in types of antipsychotics rather than to the switch itself, from antipsychotic polypharmacy to monotherapy. In 2 cases,[32,36] the addition of haloperidol or clozapine to aripiprazole resulted in QTc prolongation, and discontinuation of these adjunctive antipsychotics resolved the issue. In 5 cases,[34,35] adding quetiapine to sertindole or paliperidone to clozapine did not significantly prolong QTc intervals. In 2 case reports,[33] a switch to risperidone from amisulpride or discontinuation of amisulpride, which was used in combination with LAI antipsychotics, normalized QTc prolongation.

Discussion

Given the high prevalence of antipsychotic polypharmacy in real-world clinical practice, we conducted a systematic literature search to examine its relation with QTc interval. Notably, there is a paucity of evidence specific to this topic, which is a serious concern, given how frequently antipsychotic polypharmacy is employed. To our knowledge, there has been one systematic review on safety and tolerability issues of antipsychotic polypharmacy that included QT prolongation.[37] The authors of that review searched 2 electronic sources (PubMed and Google scholar) in October 2011, identifying 4 relevant studies, and concluded that the evidence on antipsychotic polypharmacy and QTc prolongation is mixed. Here, we used 3 electric sources (MEDLINE, Embase, and PsycINFO) in October 2014, and adopted broader key words and inclusion criteria. This resulted in more articles identified in our current systematic review (21 articles); however, it is important to note that the main conclusions from both reviews are not substantially different. Moreover, evidence is still not substantive enough to draw firm conclusions.

The findings from our current systematic review can be summarized as follows. First, the paucity of data addressing QTc interval and antipsychotic polypharmacy is worrisome in light of the frequent use of antipsychotic polypharmacy. Second, clinical trials have shown that while a combination

Table 3 Cases of corrected QT (QTc) interval prolongation with antipsychotic polypharmacy

Study	Year	Patient, age, years, and sex	Diagnosis	QTc change, ms, and antipsychotic polypharmacy (dose, mg/day)
Gurovich et al[30]	2003	66, F	SAD	450 at QTP (n/a) + CPZ (n/a), then 416 after changing them to OLZ (40)
Nandagopal et al[31]	2003	46, M	Sz	504 at RIS (2) + HPD (5), then 400 after changing them to QTP (150)
Leo et al[32]	2008	43, F	Sz	415 at APZ (30), 492 after adding HPD (5), then 428 after discontinuing HPD
Lin et al[33]	2009	37, F	Sz	510 at ASP (1400) + FPX-LAI (20), then 430 after changing ASP to RIS (n/a)
Lin et al[33]	2009	38, F	Sz	507 at ASP (1400) + HPD-LAI (50), then normalized after discontinuing ASP
Hanisch et al[34]	2010	46, M	Sz	Not increased after adding QTP (300) to SER (20)
Esslinger et al[35]	2010	25, M	Sz	Not significantly changed after adding PAL (12) to CLZ (700)
Esslinger et al[35]	2010	28, F	MS	Not significantly changed after adding PAL (9) to CLZ (700)
Esslinger et al[35]	2010	38, F	Sz	Not significantly changed after adding PAL (12) to CLZ (350)
Esslinger et al[35]	2010	27, M	SAD	Not significantly changed after adding PAL (6) to CLZ (550)
Dhillon et al[36]	2011	61, F	SAD	434–453 at APZ (30), 488–505 after adding CLZ (175), then 446–470 after discontinuing CLZ

APZ = aripiprazole; ASP = amisulpride; CLZ = clozapine; CPZ = chlorpromazine; F = female; FPX = flupentixol; HPD = haloperidol; LAI = long-acting injectable; M = male; MS = multiple sclerosis; n/a = not available; OLZ = olanzapine; PAL = paliperidone; QTP = quetiapine; RIS = risperidone; SAD = schizoaffective disorder; SER = sertindole; Sz = schizophrenia

of clozapine with risperidone, aripiprazole, or pimozide is not obviously related to an increase in QTc interval, the addition of ziprasidone or sertindole to clozapine may have the potential to prolong QTc interval. Third, among observational studies, cross-sectional investigations have demonstrated that antipsychotic polypharmacy is not clearly associated with QTc prolongation, whereas one prospective study has shown a significant increase in QTc interval following antipsychotic augmentation. Fourth, case reports do suggest a risk of QTc prolongation, at least in some patients receiving antipsychotic polypharmacy. It is possible, though, that case reports represent unusual or dramatic cases, possibly introducing bias, and do not accurately reflect true event rates and their consequences.

Beyond the limited evidence addressing antipsychotic polypharmacy and QTc interval, how the interval is calculated also warrants comment. First, most of the clinical trials and observational studies included in this review depended on QTcBZT intervals; only 2 studies[19,23] reported both QTcBZT and QTcFRD intervals. It may be ideal to report both QTc intervals, especially when the data are somewhat equivocal. Second, a QTc interval of more than 450 ms in men and more than 470 ms in women is regarded to represent clinically significant QTc prolongation.[38] In addition, a QTc interval of more than 500 ms in both men and women is related to risk of cardiac events, such as syncope, cardiac arrest, and sudden cardiac death.[39] Together with the threshold values, it is also important to consider absolute change from baseline QTc interval (that is, an increase of more than 60 ms[40]). However, these indices were not documented in numerous studies; for example, only 1 out of 10 clinical trials[16] referred to these parameters. Further, use of QTc-prolonging drugs is only one of various risk factors in QTc prolongation that also includes advanced age, female sex, history of QTc prolongation, bradykinesia, cardiac diseases, congenital long QT syndrome, hypokalemia, and hypomagnesemia.[41] As sex difference in QTc intervals is an established finding in the literature,[38,42] it would be more clinically relevant to analyze QTc intervals separately for men and women. Along similar lines, some of the studies included in our review (3 clinical trials[20,24,25] and 1 observational study[29]) excluded patients who had a history of a QTc interval of more than 450 ms or cardiac disease, limiting generalizability of results. In their comprehensive review of QTc prolongation and TdP associated with second-generation antipsychotics and antidepressants, Hasnain and Vieweg[2] pointed out these same issues as limitations.

Also note, potentially synergistic effects of antipsychotic polypharmacy on QTc intervals cannot be addressed in our systematic review. More specifically, it cannot be ruled out that a combination of lower-risk, QTc-prolonging antipsychotics can prolong QTc interval. All the clinical trials indicating that antipsychotic polypharmacy prolonged QTc interval examined augmentation of a higher-risk, QTc-prolonging antipsychotic (that is, ziprasidone or sertindole)[2,3] with a moderate-to-high-risk, QTc-prolonging antipsychotic (that is, clozapine).[2,3] Once again, the limited data available clearly underscores a need for more work on this important topic.

Limitations of our review warrant comment. Our literature search was confined to English and, as mentioned, despite a systematic literature search, only a small number of clinical trials and observational studies were identified. Further, sample sizes were small in most of the reports. As no clinical trials have examined the effects of LAI plus oral or LAI antipsychotics on QTc intervals, the current findings cannot be generalized to this formulation. Our focus here was on antipsychotic polypharmacy, but,

in clinical practice, many high-risk, QTc-prolonging psychotropics (for example, some antidepressants) are used in combination with antipsychotics. This form of psychotropic polypharmacy is also common but beyond the scope of our review. Finally, and importantly, all changes in QTc intervals may not directly translate to clinical consequences; for example, it has been shown that a so-called higher-risk medication (that is, ziprasidone) was not associated with an elevated risk of either cardiovascular mortality or sudden cardiac death relative to olanzapine in real-world use.[43] People vulnerable to life-threatening consequences of QTc prolongation are likely to exhibit decompensated repolarization reserve.[44] Importantly, clinical studies frequently exclude such frail patients with cardiac conditions, whereas this is not so with case reports. Accordingly, we need to remain somewhat cautious regarding the conclusion that we were unable to find unequivocal evidence of QTc prolongation associated with antipsychotic polypharmcy.

Conclusions

In summary, antipsychotic polypharmacy is frequently used in real-world clinical practice in the absence of solid evidence. Concurrently, the body of evidence regarding antipsychotic polypharmacy and QTc intervals is scant and inconsistent, with further studies needed. Currently available evidence fails to confirm that antipsychotic polypharmacy worsens QTc prolongation in general, although a combination of some higher-risk, QTc-prolonging antipsychotics (for example, clozapine plus ziprasidone or sertindole) may lengthen QTc intervals. A further argument for caution is the lack of robust evidence regarding efficacy with antipsychotic polypharmacy, as well as increased liability regarding numerous other unwanted side effects.[37,45] From the standpoint of QTc prolongation, special attention is warranted, particularly when antipsychotic polypharmacy is employed in patients who have other risk factors of QTc prolongation.

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