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Review article

# A systematic review of the safety and efficacy of rapid titration of quetiapine running header: Rapid titration of Quetiapine- A systematic review

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ABSTRACT

Quetiapine is a second-generation antipsychotic that is most favoured for its low propensity for extrapyramidal side effects. However, Quetiapine requires slow titration, which is disadvantageous. The brief review discussed research that trialled rapid titration of Quetiapine The author searched PubMed, Proquest, Embase, Google Scholar and Google Web using the keyword 'rapid titration' and 'quetiapine'. A total of 18 articles were included. The process, safety and efficacy of rapid titration of Quetiapine was examined. In conclusion, preliminary results appear to show that there is minimal difference in efficacy, between the rapid and traditional titration of Quetiapine. Sedation tended to occur more frequently and earlier among experimental group, and this might render rapid titration of Quetiapine to be suitable for agitated patients. There is a need for more large-scale, multisite, randomized clinical trials to examine the safety and efficacy of rapid titration of Quetiapine.

## 1. Introduction

Quetiapine is a second generation antipsychotic drug commonly utilized for bipolar disorder and schizophrenia. It is also utilised for generalised anxiety disorder, multiple sclerosis and psychosis in dementia (Taylor et al., 2015). Quetiapine consists of anxiolytic, sedative, mood-stabilising, antimanic and antidepressant properties (Chiesa et al., 2012; DeVane and Nemeroff, 2001; Vieta et al., 2010). It is likely more useful than Lithium in bipolar disorder 1 (Young et al., 2010). Among elderly, Quetiapine has a lower mortality risk as compared with various antipsychotics like Haloperidol, Risperidone and Olanzapine and (Kales et al., 2012). Quetiapine is also one of the antipsychotics with the lowest propensity for side effects such as hypoerprolactemia and extrapyramidal side effects (EPSE) and is hence favoured by both clinicians and patients. Extrapyramidal side effects encompass of dystonia, pseudo-parkinsonism, tardive dyskinesia and akathisia, which are physically debilitating and distressing for the patients (Kane, 2001; Taylor et al., 2015).

Overall, Quetiapine is a popular and commonly used drug. However, despite its advantages, Quetiapine requires long titration time, which prolongs patients' morbidity and hospitalization stay.

Quetiapine comes in either immediate or extended release. Extended release of Quetiapine can be started at 300 mg/day, and be increased to 600 mg/day by the second day. However, the extended release form is not an option for many patients as it is much more expensive than immediate-release Quetiapine. Psychiatric patients often face financial difficulties due to their chronic psychiatric conditions and inability to sustain a long-term full-time job. On the other hand, there are many generic forms of immediate release of Quetiapine that are available, which are affordable (Hallinen et al., 2012).

Unlike the extended release of Quetiapine, the immediate release of Quetiapine is initiated at a much slower titration regimen. For schizophrenia and depressive episode in bipolar disorder, Quetiapine is initiated at 50 mg/day on day 1 (Gunasekara and Spencer, 1998), 100 mg/day on day 2 and 300 mg/day on day 4. Subsequently, Quetiapine can be titrated from 300 mg/day to 750 mg/day. For patients with bipolar disorder, mania episode, Quetiapine is titrated at 100 mg/day on day 1 (Taylor et al., 2015), 200 mg/day on day 2, 300 mg/day on day 3, reaching a 400 mg/day dose on day 4. Subsequently, titration should not exceed 200 mg/day (Food and Drug Administration, 2004; Health Science Authority, 2017).

However, if Quetiapine can be titrated more rapidly, patient will suffer lesser and recover faster. Furthermore, rapid titration of Quetiapine will reduce hospitalization stay and reduces overall healthcare costs. Hence there is a need to examine the possibility and efficacy of rapid titration of Quetiapine.

Quetiapine is not without side effects. Quetiapine has a dose-response relationship (Taylor et al., 2015). Quetiapine dose was associated with the occupancy of central dopamine (Sparshatt et al., 2011). Therefore, the greater the Quetiapine dose, the more likely patients will

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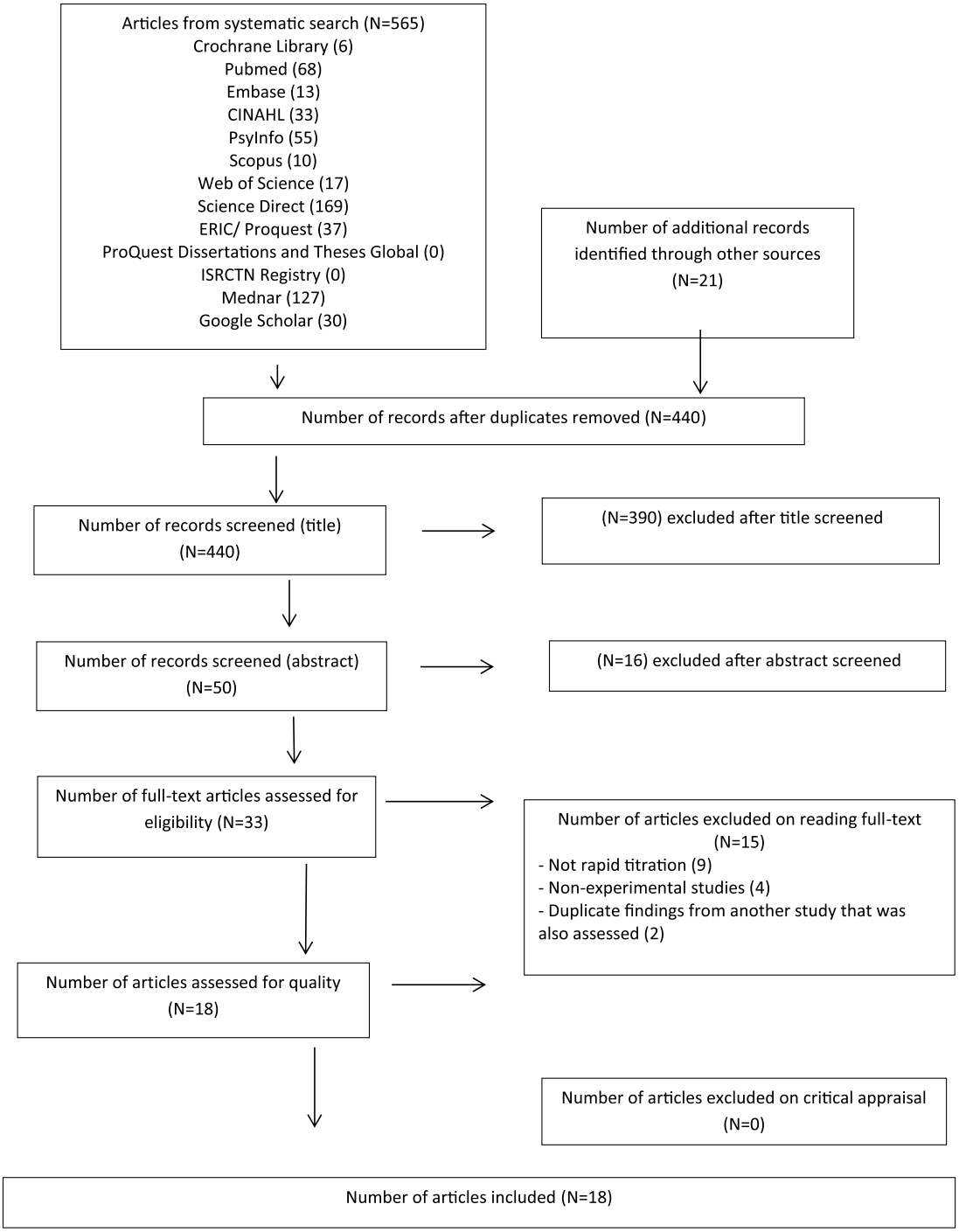


**Fig. I.** Search strategy.

experience side effects. The side effects of Quetiapine are not limited to, postural hypotension, syndrome of inappropriate antidiuretic hormone (SIADH), sedation, confusion, constipation, hepatic failure, QTc prolongation, raised fasting glucose and lipids level (Taylor et al., 2015). Therefore, the monitoring of side effects is necessary when titrating Quetiapine rapidly. Patients need to be subjectively assessed for side effects. Vital signs and postural blood pressure needs to be assessed during the initial titration of Quetiapine. Patients' blood for lipids, glucose, full blood count, liver function, prolactin, urea and electrolytes, needs to be taken for routine monitoring as per recommendations by clinical guidelines (Taylor et al., 2015). Hence, there is a need to examine the safety of rapid titration of Quetiapine.

There has not been any review that examines the possibility of rapid titration of Quetiapine, or its efficacy and safety.

**Table 1**
Characteristics of included studies - randomized controlled trials.

| Study and site | Participant characteristics | Groups | Outcomes measured | Completion/ drop-out rate | Outcomes on symptoms | Side effects |
|---|---|---|---|---|---|---|
| Hsiao et al. (2011) | Inpatients with schizophreniaor schizoaffective disorder,and CGI-S of at least 4. | 2 groups | CGI-S, PANSS, side effects, BARS, SARS | (13%) in RTG did not complete due to worsening condition, $n = 3$ and hypersomnia $n = 1$. | RTG had sig reduced in PANSS. Only RTG had sig PANSS and CGI-S reduction til end of study. | 93.3% of RTG and 80% of CTG reported side effects. Constipation was sig greater in the RTG. |
| Taiwan Chang Gung Memorial Hospital | Sedatives and psychotropic medications that were taken for at least 4 weeks before the study was allowed. | 30 in rapid titration group (RTG), $n = 30$: | | 30% in CTG did not complete, $n = 3$, because of worsening condition, $n = 1$, and consent withdrawal, $n = 2$. | | EPSE and hypersomnia was not sig different between the 2 groups. |
| | | D1: 200 mg | | | | Electrocardiography, vital signs, postural blood pressure, and the prevalence of EPSE, adverse events among the groups are not significant. |
| | | D2: 400 mg<br>D3: 600 mg<br>D4: 800 mg<br>D5–D14: 400 mg–800 mg | | | | |
| | | Conventional titration group (CTG), $n = 10$ | | | | |
| Mohammad et al. (2014) | Inpatients aged 18–60 years old, with agitation and PANSS-EC at least 15 | Two groups | PANSS-EC, CGI-C. | NA | No significant differences for PANSS-EC. CGI-C significantly reduced for controlled group ($p = 0.07$). | Adverse effect profiles similar. Sedation most common. 11 of 34 in controlled group and 12/38 in treatment group had low diastolic blood pressure. |
| USA Psychiatric emergency | Concomitant medications not stated. | 1. 300 mg oral Quetiapine | | | | No syncope, EPSE and hypotensive collapse noted. |
| | | 2. I/M Haloperidol 5 mg, 2 mg I/M Benztropine mesylate and 2 mg I/M Lorazepam. | | | | |
| Pae et al. (2005a) | Inpatients with bipolar mania | 2 groups Rapid titration group (RTG): | YMRS, CGI-S, vital signs, ECG, laboratory tests. BARS, SARS. | 3 dropped out due to sedation, RTG ($n = 2$) and CTG (n-1). | YMRS and CGI-S improved overtime, but no sig difference between both groups. | Side effects were dry mouth (RTG 69.2%, CTG 85.7%), sedation (RTG 38.5%, CTG 57.1%), Headache (RTG 30.8%, CTG 28.6%), dizziness (RTG 23.1%, CTG 14.3%) and postural hypotension (RTG 15.4%, CTG 14.3%). |
| Korea Hospital | Mood stabilizers and benzodiazepine taken > 4 weeks at were Continued and titrated. | D1: 200 mg | | | | Sedation occurred earlier in RTG. |
| | | D2: 400 mg | | | | No sig different in ECG, laboratory tests, SARS and BARS scores between both groups. |
| | | D3: 600 mg<br>Conventional titration group (CTG)<br>D1: 50 mg<br>D2: 100 mg<br>D3: 200 mg<br>D4: 300 mg<br>D5: 400 mg | | | | |

(*continued on next page*)

**Table 1** (*continued*)

| Study and site | Participant characteristics | Groups | Outcomes measured | Completion/ drop-out rate | Outcomes on symptoms | Side effects |
|---|---|---|---|---|---|---|
| Pae et al. (2005b) | Participants with acute schizophrenia | 2 groups Rapid titration group (RTG): | PANSS, PANSS-EC, CGI-S, BARS, SARS, adverse events | 2 in RTG dropped out due to sedation. | RTG group had sig greater reduction in PANSSEC scores at Day 4 (36.4% vs 13.1%) and Day 5 (39.9% vs 15.3%) as compared with the CTG ($p < 0.05$). | Sedation were experienced by 36.7% of RTG and 22.2% of CTG. Dizziness were experienced by 20% of RTG and 0% of CTG. |
| Korea hospital | Concomitant medications not stated. | D1: 200 mg<br>D2: 400 mg<br>D3: 600 mg<br>D4: 800 mg,<br>From D5: 400–800 mg,<br>$n = 40$<br>Conventional titration group (CTG)<br>D1: 50 mg<br>D2: 100 mg<br>D3: 200 mg<br>D4: 300 mg<br>D5: 400 mg<br>From D6: 400–800 mg | | 1 in CTG withdrew consent. | | However, there were no significant differences in any side effects between the 2 groups such as EPSE, sedation and dizziness. No significant differences in ECG, weight, vital sights and laboratory results between the 2 groups. |
| Smith et al. (2005) | 69 inpatients aged 18 to 64 years with PANSS of at least 60, CGI-S of at least 4 | 3 groups | Physical examinations, vital signs, laboratory tests, ECG subjective interviews for symptoms | 3 of 69 withdrew due to agitation. | Nil | Vital signs, laboratory results and ECG were similar among the 3 groups. ECG showed increased in ventricular rate. |
| USA Multicenter | 2 days drug-washout period | Group A: 5 days til 400 mg, $n = 22$<br>Group B: 3 days til 400 mg, $n = 22$<br>Group C: 2 days til 400 mg, $n = 25$ | | | | The frequency of side effects were similar among the 3 groups: hypotension, $n = 14$; 20.9%, postural hypotension, $n = 12$;17.9%, tachycardia, $n = 7$;10.4%, hypertension, $n = 5$, 7.4%, bradycardia, $n = 3$,4.4%. 1 syncope was treatment-related. |

**Groups:** Day (D).
**Outcome measures:** Barnes Akathisia Rating Scale (BARS); Clinical Global Impression of Change (CGI-C); Clinical Global Impression Severity (CGI-S); Montgomery-Asberg Depression Rating Scale (MADRS); Positive and Negative Syndrome Scale (PANSS); Positive and Negative Syndrome Scale –Excited Component (PANSS-ES); Simpson-Angus Rating Scale (SARS); Young Mania Rating Scale (YMRS).
**Side effects:** EPSE (Extrapyramidal side effects); ECG (Electrocardiogram); Sig (Significantly).

**Table 2**
Characteristics of included studies – Quasi-experimental studies.

| Study and site | Participant characteristics | Groups | Outcomes measured | Drop-out rate/ dose reduction rate due to side effects | Outcomes on symptoms | Side effects |
|---|---|---|---|---|---|---|
| Cakir et al. (2008) | Inpatient with acute mania | Single group | YMRS, PANSS- ES | Nil | YMRS score reduced from baseline 39 to 21.3 on D7. PANSS reduced from 28.5 to 14.5. | No side effect noted. |
| Istanbul Inpatient setting | Concomitant medications not stated. | D1: Mean dose 2400 mg.<br>- 300 mg oral quetiapine every 3 h until sedated.<br>D7: 1350 mg | | | Agitation significantly reduced from day 1. | |
| Constant et al. (2009) | Inpatients aged > 18 years old who stayed for at least 7days, with bipolar I and YMRS score of >19, CGI-S >3, $n = 29$. | Single group | YMRS, CGI-S, BARS, SAS, secondary safety outcomes. | 100% completion. | YMRS score decreased from baseline of 29.7 (7.8) to 11.8 (9.6) on D21 ($p < 0.001$). | 79.3%, $n = 23$ reported 58 side effects, with 13.5%, $n = 4$ reporting 9 severe side effects. 21%, $n = 6$, sedation, while 10%, $n = 3$ experienced dizziness, somnolence and constipation. Other side effects were hypotension, 17%, $n = 5$, dry mouth, 14%, $n = 4$ and headache. |
| | | D1: 200 mg/d<br>D2: 400 mg/d<br>D3: 600 mg/d<br>D4: 800 mg/d<br>D5: 400–800 mg/day | | 1 patient- temporary discontinuation due to hypotension at D1 (quetiapine dose 200 mg/day). | CGI-S decreased significantly from baseline of 5.4 (0.8) to 2.9 (1.4) on D21. | BARS scores reduced among 48% ($n = 13$) and SAS scores reduced among 46% ($n = 12$) of participants. |
| Belgium 13 study sites | No other antipsychotic allowed.<br>Mood stabilizers, antidepressants taken > 4 weeks were continued.<br>Benzodiazepine continued. | | | Due to side effects, dosage was reduced in 8 participants for sedation, $n = 6$, hypotension, $n = 1$ and hypokinesia, dry mouth, vertigo, vomiting and muscle rigidity, $n = 1$. | | ECG, vital signs were unremarkable. |
| Hatim et al. (2006) | 20 inpatients with mania | Single group | YMRS, PANSS, CGI, side effects | 25% dropped out due to agitation ($n = 3$), depression ($n = 1$) and loss to follow-up ($n = 1$). | YMRS, PANSS, and CGI-S scores decreased by 48% ($p < 0.05$), 19% ($p < 0.05$), and 73%, respectively. | 80%, $n = 16$ reported side effects. |
| Malaysia Hospitals | Mood stabilizers and benzodiazepine taken >4 weeks at were continued.<br>Other antipsychotic drugs were stopped from D3. | D1: 200 mg<br>D2: 400 mg<br>D3: 600 mg<br>D4: 800 mg<br>D5: 400 mg–800 mg | | 35%, $n = 7$ had dose adjustment due to 14 side effects. | | 70% experienced postural blood pressure drop, $n = 15$, despite only one significant postural drop. Other side effects were not limited to tremor, $n = 6$, agitation, $n = 3$, and $n = 2$ for constipation, dry mouth, musculoskeletal stiffness, somnolence and salivary hypersecretion. |
| Scheffer et al. (2010) | 75 outpatients aged between 6 −16 years old, with manic or hypomanic episodes. | Single group | YMRS, CGI-I, (SEFCA), vital signs, weight, side effects | Missing outcome data for 40% of participants due to prompt clinical response or change of service provider. | YMRS score reduced by 50% among 79% ($n = 59$)of the participants. CGI-I score = <2 among 90% ($n = 67$) of the participants. | 50% of participants had sedation, mean weight gain of 3 pounds. |

(*continued on next page*)

**Table 2** (*continued*)

| Study and site | Participant characteristics | Groups | Outcomes measured | Drop-out rate/ dose reduction rate due to side effects | Outcomes on symptoms | Side effects |
|---|---|---|---|---|---|---|
| USA Clinics | Concomitant stimulants and mood stabilizers allowed. | D1: 100 mg<br>D5: 400 mg | | | | No postural hypotension.<br>No changes in systolic blood pressure, |
| Peuskens et al. (2008) | Inpatient, > 18 years old with schizophrenia/ schizoaffective disorder, who stayed for at least 7days, Other antipsychotic drugs were discontinued by 2 days into recruitment. | Single group | PANSS, CGI-S, BARS, SARS, dropouts, side effects, ECG, vital signs | 1 discontinuation- prolonged QTcB interval on D5, 2 dropped out due to non-compliance. | PANSS score | No serious adverse effects. |
| Belgium Multi-center | Antidepressants and mood stabilizers were allowed. | D1: 200 mg.<br>D2: 400 mg<br>D3: 600 mg<br>D4: 800 mg.<br>Next 10 days: 400–800 mg | | | decreased sig from 92.8 to 78.4 ($p < 0.001$).<br>CGI-S score decreased sig from 4.7 to 3.8 ($p < 0.001$). | Physical examination found no clinically relevant changes from baseline. There were no consistent changes over time in vital signs. BARS and SAS were reduced overtime.<br>29 side effects reported among 12 participants.<br>The most commonly reported adverse events (AE) were gastrointestinal complaints, $n = 4$, dizziness $n = 3$, somnolence $n = 3$ and $n = 2$ for dry mouth, agitation, hypotension and QTC prolongation. |
| Yoon et al. (2008) | Participants with bipolar I disorder, $n = 79$. | Single group<br>D1: 200 mg/d, rapidly titrated to 800 mg/day in the first week. | YMRS, MADRS, BPRS, SAS, BARS, DAI-10, SRDS | 27.8% dropped out, $n = 23$. | Mean mania, depressive and psychotic scores were significant at days 7, 14, 21 and 42 from baseline. | Drug-induced parkinsonism and akathisia: no significant difference from baseline |
| Korea multicenter | Concomitant medications not stated. | | | | | |

**Groups:** Day (D).
**Outcome measures:** Barnes Akathisia Rating Scale (BARS); Clinical Global Impression Improvement (CGI-I); Clinical Global Impression Severity (CGI-S); Drug Attitude Inventory (DAI-10); Global Assessment of Functioning Scale (GAF); Positive and Negative Syndrome Scale (PANSS); Positive and Negative Syndrome Scale –Excited Component (PANSS-ES); Side-Effects for Children and Adolescents (SEFCA); Simpson-Angus Rating Scale (SARS); Subjective Response to Drug Scale (SRDS); Young Mania Rating Scale (YMRS).
**Side effects:** ECG (Electrocardiogram); Sig (Significantly).

**Table 3**
Characteristics of included studies - case reports .

| Study country | Setting/context | Participants characteristics | Description of main results |
|---|---|---|---|
| Lin et al. (2008) | Prescribe Quetiapine 200 mg ON from a general physician clinic. 2 h later, developed drowsiness and sent to emergency department. | 22year old Chinese man experienced aloofness, alogia, social isolation for 3 months. Given Quetiapine 200 mg for suspected schizophrenia. 2 h later, developed drowsiness and sent to emergency department. | Laboratory examination was normal, except K was 2.8 mmol/L, indicating hypokalemia. Quetiapine discontinued, supporative treatment with IV K in ICU. Fully recovered, with K 3.7 mmol/L. |
| Taiwan | | | Pt attempted suicide by taking 600 mg Quetiapine 2 months after discharge. Disturbance of consciousness, K was 3.6 mmol/L from 2.9 mmol/L after K replacement. Dopamine agonists may increase ADH levels. |
| Ozkaya et al. (2012) | Psychiatry polyclinic prescribed 200 mg Quetiapine, then present to Urology clinic for priapism 3days later. | A 68-year-old male patient with insomnia, given a single dose of 200 mg Quetiapine for insomnia by Psychiatry. Developed involuntary erection and pain began in the penis, 6hours after first dose of Quetiapine. | Pt has Ischemic priapism. No detumescence after needle aspiration of corpus cavernosum and injection of diluted intracavernosal adrenalin. Distal spongio-cavernosal shunt surgery was performed, and 25 mg sildenafil was administered. 30% of priapism cases are related to drug, and atypical antipsychotics causes 50% of the cases. |
| Turkey | | | |

Potassium (K).

## 2. Methods

The review was conducted according to the Joanna Briggs Institute (JBI) guidelines for systematic review report writing (Joanna Briggs Institute, 2016).

### 2.1. Search strategy

Firstly, the authors conducted an initial limited search of MEDLINE and CINAHL using the key words 'rapid titration' AND 'Quetiapine'. This search found initial articles. The keywords and subject headings of those articles were perused, leading to an identification of all search keywords. The keywords subsequently utilized 'high dose' AND 'Quetiapine', 'rapid titration' AND 'Quetiapine', 'fast titration' AND Quetiapine, 'rapid escalation' AND Quetiapine.

Secondly, using the identified keywords, the authors searched eleven databases (Cochrane Library, Proquest, Embase, Google Scholar, CINNAL, ScienceDirect, Medline, Scopus, PsycInfo, Web of Science, and Mednar). The search for unpublished studies included: SpringerLink thesis database and Randomized Control Trial Registry Website. Thirdly, the reference list of all identified reports and articles were searched for the possibility of additional included studies. All articles published before May 2017 were included.

### 2.2. Study selection

Each study was independently scrutinized by a reviewer. Studies were included if psychiatric patients were taking a faster titration of Quetiapine. Studies were included if Quetiapine dose was more than 50 mg on day 1 for participants with schizophrenia and more than 100 mg on day 1 for participants with mania. Case reports, case series and experimental studies (quasi-experimental studies and randomised controlled trials) were also included. Studies in English were included. Studies were excluded if full publications were unavailable.

### 2.3. Quality assessment

Studies were evaluated for methodological quality by two reviewers independently using tools appropriate to articles' methodology. In cases of discrepancies, a third reviewer reviewed the article. Appraisal tools utilized were the Joanna Briggs Institute Critical Appraisal tool for case report, case series, randomised controlled trials and quasi-experimental studies (The Joanna Briggs Institute, 2017).

### 2.4. Data extraction

Data was extracted using the standardized data extraction tools in JBI SUMARI by two independent reviewers. The data extracted included specific details about the rapid Quetiapine titration, types of participants, methods, outcome measurement and results. Disagreements were resolved a third reviewer. Authors of papers were contacted to request missing or additional data where required.

### 2.5. Analysis

We propose to illustrate an overview of the process, safety and efficacy of rapid Quetiapine titration. Statistical pooling was not possible due to the heterogeneity of the interventions, study designs and outcome (The Joanna Briggs Institute, 2014). Hence, the findings would be presented in narrative form using tables.

## 3. Results

### 3.1. Search results

Literature review identified 565 hits. Screening of reference list identified a further 21 studies. After duplicate elimination, 440 articles were left. Screening of title and abstract excluded 390 and 16 articles, respectively. Thirty-three full texts were retrieved for examination. Eighteen studies were included eventually. Fifteen articles were excluded. Reasons for exclusion are presented in Fig. I.

### 3.2. Description of studies

#### 3.2.1. Characteristics of included studies

There were 18 articles. The research design ranged from randomised controlled trials, quasi-experimental, case report, case series to discursive paper. Six studies had adopted a single-group design (Cakir

**Table 4**
Characteristics of included studies - case series form.

| Study and site | Participant characteristics | Titration of Quetiapine | Outcomes measured | Drop-out rate/ dose reduction rate due to side effects | Outcomes on symptoms | Side effects |
|---|---|---|---|---|---|---|
| Beer et al. (2007) | 23 inpatients with Schizophrenia, schizoaffective disorder | 2 groups | Physical examination, ECG, EEG vital signs, CGI-S | Mild rigor and hypokinesia in change over group, $n = 1$, stopped after Quetiapine reduced from 600 mg to 500 mg. | In change over group, CGI-S reduced from 4.759 +/− 0.87 to 2.929 +/− 0.67 ($p < 0.002$). | No pathological EEG and ECG changes in both groups. |
| Germany Inpatient setting | Benzodiazepines and mood stabilizers allowed. None in Group B took another antipsychotic | Group A: change over from other antipsychotic, $n = 12$<br>Dosage range:<br>400 mg–1000 mg | | | In Group B, CGI-S reduced from 6 +/− 0.63 to 4 +/− 0.77 ($p < 0.001$). | In change over group, side effects were sedation, $n = 4$, tachycardia, $n = 4$, elevated transaminases, $n = 8$, transient raised eosinophils, $n = 2$.<br>In group B, side effects were sedation, $n = 3$, vertigo, $n = 2$, tachycardia, $n = 7$, constipation, $n = 3$ and xerostomia, $n = 3$., elevated transaminases, $n = 7$, raised eosinophils, $n = 2$, decreased leucocytes, $n = 2$. |
| | | Group B: directly treated with Quetiapine, $n = 11$<br>D2–D6: 600 mg | | | | |
| Oral et al. (2005) | 10 participants- rapid titration (3 hospitalized, 7 outpatients) | 10 participants. | CGI-BP and YMRS, side effects: sedation, | Nil | YMRS and CGI-BP reduced by 50% within one week in both groups. | 5 had sedation, that was sig greater in group B. |
| Turkey Hospital | | 2 groups<br>Group A: 300 mg dose increment every 3 days.<br>Group B: 300 mg dose increment daily up to 600–1200 mg /d. | | | | 1 had edema that spontaneously resolved.<br>3 participants did not report side effects. |
| Pajonk et al. (2006) | 8 inpatients; 5 with schizophrenia and 3 with mania | D1: 200–300 mg | PANSS, YMRS, CGI-S, GAF | 1 dropped out due to somnolence, increased confusion and sedation. | PANSS, YMRS and CGI-S scores reduced. GAF scores increased. | Four experienced fatigue, with one dropping out. One had blood pressure fell to 90/60 mmHg from 130/80 mg.<br>Four did not report any side effects. |
| Germany Saarland University Hospitals | | D2: 400–900 mg<br>D3: 350–900 mg<br>D4: 450–800 mg<br>D5: 300–800 mg<br>D6: 300–1000 mg<br>D7: 300–1200 mg | | | | |

**Groups:** Day (D); Intramuscular (I/M).
**Outcome measures:** Clinical Global Impression Bipolar disorder (CGI-BP); Clinical Global Impression Severity (CGI-S); Positive and Negative Syndrome Scale (PANSS); Positive and Negative Syndrome Scale –Excited Component (PANSS-ES); Simpson-Angus Rating Scale (SARS); Young Mania Rating Scale (YMRS).
**Side effects:** ECG (Electrocardiogram); EEG (Electroencephalography); Sig (Significantly).

**Table 5**
Characteristics of included studies - text and opinion study form.

| Study | Type of text | Population represented | Topic of interest | Setting/context/ culture | Stated allegiance/position | Description of main argument(s) |
|---|---|---|---|---|---|---|
| Arango and Bobes (2004) | Opinion | Participants with acute schizophrenia symptoms including aggression and anxiety | More rapid initiation of Quetiapine in participants with symptoms of aggressive, anxiety and hostility. | During acute exacerbation or emergemcies | Rapid Quetiapine initiation can provide safe, effective treatment in inpatients with acute schizophrenia. | Quetiapine has an excellent tolerability profile that enhances patient adherence to medication. It is recommended as a first-choice antipsychotic for acute schizophrenia exacerbations. |
| Peuskens et al. (2007) | Text and Opinion | hospitalized participants with acute schizophrenia or bipolar disorder | Consensus on appropriate treatment strategies | Acute hospital | Rapid initiation of quetiapine in participants with acute psychosis or mania is effective and well tolerated. | Oral atypical antipsychotics should be a first-choice medication for acutely ill cooperative inpatients. A positive initial treatment experience can improve patient compliance and treatment adherence. |

et al., 2008; Constant et al., 2009; Hatim et al., 2006; Pseuskens et al., 2008; Scheffer et al., 2010, Yoon et al., 2008). Five studies adopted >2 group design (Hsiao et al., 2011; Mohammad et al., 2014; Pae et al., 2005a; Pae et al., 2005b; Smith et al., 2005). Participants were adolescents, children, and young adult, who suffered from bipolar mania or schizophrenia. Studies were conducted in Taiwan ($n$ = 2), USA ($n$ = 3), Korea ($n$ = 3), Belgium ($n$ = 2), Turkey ($n$ = 2), Istanbul ($n$ = 1), Malaysia ($n$ = 1), Germany ($n$ = 2). In addition, there were two discursive papers, adding to a total of 18 articles. Please refer to Tables 1–5.

### 3.3. Risk of bias

In view of the limited studies available, all studies were included. The quality of the studies was modest (See Appendices 1–5). Firstly, there are limited randomised controlled trials conducted on this topic. Many studies utilized case reports, case series and quasi-experimental research designs. Secondly, most studies utilised small samples and most recruited participants from a single site. These limit generalisability. Thirdly, in some studies, some participants are taking concomitant medications such as antipsychotics, sedatives or mood stabilizers. Hence, effects of such concomitant medications may confound study findings.

## 4. Effects on outcome domains

### 4.1. Safety of rapid titration of Quetiapine; drop-out rates

Please see Tables 1–5. Among the four randomised controlled trials that reported drop-out rates, participants in the experimental group were at a greater risk of drop-out from side effects (Pae et al., 2005a,b; Smith et al., 2005), with the exception of research by Hsiao et al. (2011). Among the randomised controlled trials, drop-out rates were due to sedation in two research studies (Pae et al., 2005a,b). In one research, drop out was due to agitation (Simth et al., 2005).

Among the quasi-experimental studies, drop out reasons were due to hypotension (Constant et al., 2009), agitation (Hatim et al., 2006), depression (Hatim et al., 2006), prolonged QTcB (Peuskens et al., 2008).

Among the case report studies, one participant experienced severe hypokalaemia presenting as drowsiness after one dose of Quetiapine 200 mg (Lin et al., 2008). In another case report, participant experienced priapism after single dose of Quetiapine 200 mg (Ozkaya et al., 2012). Among the case series, drop out reasons were hypokinesia (Beer et al., 2007) and sedation (Pajonk et al., 2006).

### 4.2. Safety of rapid titration of Quetiapine; side effects

Please see Tables 1–5. Among the randomised controlled trials, participants in the experimental group appeared to experience a greater risk of side effects such as constipation (Hsiao et al., 2011), low blood pressure and sedation. Sedation also appeared sooner in the experimental group.

Vital signs, laboratory tests, electrocardiogram and rates of extrapyramidal side effects tended to be similar between both groups (Hsiao et al., 2011; Pae et al., 2005a,b). Side effects profile seems to be similar between the two groups (Mohammad et al., 2014; Pae et al., 2005b). Although sedation and dizziness were experienced by more participants in the rapid titration group, the difference were not significantly different (Pae et al., 2005b).

Among the quasi-experimental studies, notable side effects were sedation (Constant et al., 2009; Scheffer et al., 2010), dizziness (Constant et al., 2009; Peuskens et al., 2008), somnolence (Constant et al., 2009; Hatim et al., 2006; Peuskens et al., 2008), constipation (Constant et al., 2009), headache (Constant et al., 2009), hypotension (Constant et al., 2009; Hatim et al., 2006; Peuskens et al., 2008) dry mouth (Constant et al., 2009; Hatim et al., 2006; Peuskens et al., 2008),

agitation (Hatim et al., 2006; Peuskens et al., 2008), muscle stiffness, tremors (Hatim et al., 2006) weight gain (Scheffer et al., 2010) prolonged QTC (Peuskens et al., 2008), and gastrointestinal side effects (Peuskens et al., 2008). Although three studies found hypotension as a side effect, Scheffer et al. (2010) reported no postural hypotension. Extra-pyramidal side effects were reduced overtime in the single group studies (Constant et al., 2009; Peuskens et al., 2008).

In the case series studies, sedation was significantly greater in one study (Oral et al., 2005). Besides side effects mentioned above, other side effects were elevated transaminases and eosinophils (Beer et al., 2007).

### 4.3. Efficacy of rapid titration of Quetiapine

Please see Tables 1–5. Among the five randomised controlled trials studies, only four examined the efficacy of rapid titration of Quetiapine. Psychotic symptoms were significantly reduced in the rapid titration group, as compared to controlled group in two studies (Hsiao et al., 2011; Pae et al., 2005b), but not two other studies (Mohammad et al., 2014; Pae et al., 2005a). The results were equivocal, with two studies having significant findings and two without. However, in Pae et al. (2005b), the significant reduction was only in day 4 and day 5. Furthermore, in the study by Mohammad et al. (2014), the CGI-C (Clinical Global Impression of Change) was conversely, significantly reduced for controlled group. However, in terms of rigorousness of research design, the study by Mohammad et al. (2014) achieved allocation concealment and blinding of participants. Maniac, psychotic symptoms among participants were reduced in the quasi-experimental and case series studies.

## 5. Discussion

Vital signs and postural blood pressure needs to be assessed during the initial titration of Quetiapine. Patients' blood needs to be taken for routine monitoring as per recommendations mentioned above (Taylor et al., 2015). Further large-scale, multisite, randomized clinical trials will do well to include comparison group with larger sample sizes. Such research can explore whether side effects between the conventional and rapid titration groups are significantly different in terms of quantity, frequency and duration. Targeted side effects that are of note from this systematic review are sedation, dizziness, hypotension, somnolence, constipation, dry mouth and agitation. Further research could examine the participants' intrapersonal variables that make them vulnerable to specific side effects, such as gender, age, race, geographical location, prior antipsychotic usage and response, liver function and levels of specific enzymes including CYP3A4.

Sedation tended to occur more frequently and earlier in the experimental group. On a positive note, this might render Quetiapine suitable as a means of sedation for actively psychotic or manic symptoms. This was explored in two studies (Cakir et al., 2008; Mohammad et al., 2014), and preliminary findings found oral Quetiapine a useful substitute for the traditional intramuscular sedation. However, further research also needs to explore the relationship between Quetiapine and agitation. In terms of efficacy, preliminary results appear to show that there is minimal difference between rapid and traditional titration of Quetiapine.

In summary, cases of drop-out or dose reduction were due to intolerability of side effects. Hence, rapid titration of Quetiapine is subjected to individual's tolerability. Rates of drop-out and side effects seem to be similar among both control and intervention groups. Rapid titration of Quetiapine seems suitable as a means of sedation. However, existing research utilized non-randomized designs and small sample sizes, and research results cannot be deemed conclusive.

### 5.1. Recommendations

The effectiveness of rapid titration of Quetiapine had equivocal findings. In terms of side effects, rapid titration of Quetiapine resulted in increased side effects such as constipation, low blood pressure and sedation. Therefore, the findings of this systematic review do not support rapid titration of Quetiapine. However, faster titration of Quetiapine is recommended if sedation was desired during treatment, such as when treating a particularly aggressive patient. Besides such cases, rapid titration of Quetiapine is not recommended at this point of time.

## 6. Conclusion

In conclusion, this is the first review that explores the process, safety and efficacy of rapid titration of Quetiapine. Preliminary results appear to show that there is minimal difference in efficacy between the rapid and traditional titrations of Quetiapine. There is a need for more large-scale, multisite, randomized clinical trials that recruits large sample sizes, to better explore the safety and efficacy of rapid titration of Quetiapine.

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## Declaration of Competing Interest

None.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.112557.

## Appendix 1. Randomised controlled trial

| Bias | 1. Randomisation process | 2. Allocation concealment | 3. Similarities at baseline | 4. Blinding participants | 5. Blinding interventionists | 6. Blinding outcome assessors | 7. Similarity of treatment between groups | 8. Attrition follow-up | 9. Groups analyzed in their specific groups | 10. Simliarity of outcomes for different groups | 11. Reliability of outcomes | 12. Appropriate statistical analysis | 13. Appropriateness of trial design |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Authors** | | | | | | | | | | | | | |
| Hsiao et al. (2011) | + | + | ++ | − | − | + | ++ | ++ | ++ | ++ | ++ | ++ | ++ |
| Mohammad et al. (2014) | + | ++ | ++ | ++ | + | + | ++ | ++ | − | ++ | ++ | ++ | ++ |
| Pae et al. (2005a) | + | + | ++ | + | + | + | ++ | ++ | ++ | ++ | ++ | ++ | ++ |
| Pae et al. (2005b) | + | + | + | + | + | + | ++ | ++ | ++ | ++ | ++ | ++ | ++ |
| Smith et al. (2005) | + | + | ++ | ++ | ++ | + | ++ | + | ++ | ++ | ++ | ++ | ++ |

## Appendix 2. Quasi-experimental studies

| Bias | 1. Intervention determined effect? | 2. Similarities at baseline | 3. Similar care rendered to participants? | 4. Presence of control group | 5. Multiple measurements pre-post intervention? | 6. Attrition follow-up | 7. Outcomes measured similarly between groups? | 8. Reliability of measurements | 9. Appropriateness of statistical analysis |
|---|---|---|---|---|---|---|---|---|---|
| **Authors** | | | | | | | | | |
| Cakir et al. (2008) | ++ | NA | + | − | ++ | ++ | NA | ++ | ++ |
| Constant et al. (2009) | ++ | ++ | ++ | − | ++ | + | ++ | ++ | ++ |
| Hatim et al. (2006) | ++ | ++ | ++ | − | ++ | + | ++ | ++ | ++ |
| Peusken et al. (2008) | ++ | ++ | ++ | − | ++ | + | ++ | ++ | ++ |
| Scheffer et al. (2010) | ++ | ++ | ++ | − | ++ | + | ++ | ++ | ++ |
| Yoon et al. (2008) | ++ | ++ | ++ | − | ++ | − | ++ | ++ | ++ |

## Appendix 3. Case reports

| Bias | 1. Clear description of demographic characteristics | 2. Patient's history clearly described and presented as a timeline? | 3. Clear description of patient's clinical condition | 4. Clear description of diagnostic tests, assessment methods and results | 5. Clear description of interventions or treatment procedures | 6. Clear description of clinical condition post-intervention | 7. Adverse or unanticipated events clearly identified and described? | 8. Does the case report provide take-away lessons? |
|---|---|---|---|---|---|---|---|---|
| **Authors** | | | | | | | | |
| Lin et al. (2008) | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ |
| Ozkaya et al. (2012) | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ |

## Appendix 4. Case series

| Bias | 1. Clear inclusion criteria | 2. Outcome measurments valid, reliabile and standard | 3. Complete and consecutive inclusion of participants? | 4. Clear description of demographic characteristrics | 5. Clear despcription of patients' clinical information | 6. Clear reporting of follow-up results or outcome | 7. Clear definition of disease/ condition of interest | 8. Clear reporting of the demographic data of presenting clinic (s)/ site(s) | 9. Appropriateness of statistical analysis |
|---|---|---|---|---|---|---|---|---|---|
| **Authors** | | | | | | | | | |
| Beer et al. (2007) | ++ | ++ | − | ++ | ++ | ++ | ++ | ++ | ++ |
| Oral et al. (2005) | ++ | ++ | + | − | − | + | ++ | − | ++ |
| Pajonk et al. (2006) | ++ | ++ | ++ | ++ | ++ | ++ | ++ | ++ | NA |

## Appendix 5. Text and opinion study

| Bias | 1. Clear identification of opinion source | 2. Does the source of opinon have standing in the field of expertise? | 3. Are the interests of the relevant population the central focus of the opinion? | 4. Is the stated position the result of an analytical process, and is there logic in the opinion expressed? | 5. Reference to the extant literature? | 6. Logical defence of incongruency with sources/ literature |
|---|---|---|---|---|---|---|
| **Authors** | | | | | | |
| Arango and Bobes (2004) | + + | + + | + + | + + | + + | + + |
| Peusken et al. (2007) | + + | + + | + + | + + | + + | + + |

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