REVIEW ARTICLE

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Quetiapine and Paediatric Psychiatrica: *Evidence or Diffidence?*

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ABSTRACT *~ The atypical antipsychotic, quetiapine has been on market for years now with long track record. In child and adolescent psychiatry, it is FDA-approved for childhood-onset schizophrenia and juvenile bipolar mood disorder. Its attractive pharmacological portfolio speaks to the idea of a versatile pluripotent broad-spectrum psychotropic agent expanding its therapeutic potential on clinical grounds. In this focussed review, authors brief these clinical indications whilst examining the extant evidence.*
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Quetiapine fumarate, a benzothiazepine, low-potency atypical antipsychotic, $5HT_{2A}$-D_2 antagonist, has been on market for years now with long track record. In child and adolescent psychiatry, it is FDA-approved for childhood-onset schizophrenia and juvenile bipolar mood disorder. Its attractive pharmacological portfolio speaks to the idea of a versatile pluripotent broad-spectrum psychotropic agent expanding its therapeutic potential on clinical grounds. In this focussed review, we would brief these clinical indications whilst examining the extant evidence.

Childhood-Onset Schizophrenia

Quetiapine is FDA-approved for schizophrenia age 13 and above based on a single 4-week RCT.[1] Interestingly, in this trial, there was a tangible improvement on the anhedonia-asociality subscale of SANS at 200 mg dose. Authors concluded that, in contrast to multiepisode patients, an initial dose of 250 to 300 mg/day of quetiapine is proposed as a primary target dose in drug-naive first-episode psychosis patients.

Another RCT from Denmark,[2] with an active comparator, aripiprazole, both were equally effective but differs in tolerability (metabolic syndrome in the former vs. motoric/akathisia and unexpectedly sedation in the latter).

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Juvenile Bipolar Mood Disorder

Quetiapine is FDA-approved for children with acute mania aged 10 and above. This is based on one 3-week RCT.[3] Significant improvement in YMRS score versus placebo was first observed at day 4 with quetiapine 400 mg/d and day 7 with quetiapine 600 mg/d. Mean changes in body weight at day 21 (observed cases) were 1.7 kg for both quetiapine doses and 0.4 kg for placebo. Another supporting RCT,[4] with an active comparator, valproate, both were equally effective, though a quicker reduction of manic symptoms may occur with quetiapine as compared with valproate. Of note, quetiapine is *not* approved for bipolar depression in children, unlike the case in adults. It failed 2 RCTs.[5]

Disruptive Behavioural Disorders

We could locate a single RCT[6] where quetiapine improved adolescent aggression in the context of conduct disorder. The final mean dose of quetiapine was 294 ± 78 mg/day. This was earlier demonstrated in an open-label trial[7] with the mean dose at week 8 was 4.4 mg/kg. Interestingly, this trial was followed by an 18-week extension phase[8] where response of quetiapine was well-sustained and well-tolerated. The median quetiapine dose at end of study was 150 mg/day.

Another open-label trial[9] showed a favourable response to add-on quetiapine when methylphenidate monotherapy failed to address aggressivity in ADHD.

An open-label trial[10] echoed these positive results in youths with bipolar II disorder and aggressive behaviours. The mean final dose was 258 ± 124 mg/day.

In the same vein, Naguy[11] reported on an interesting case of ADHD where quetiapine adjuventia did not only offset methylphenidate-related appetite suppression and initial insomnia, but also tackled comorbid social anxiety, tics, and enuresis while complementing cognitive response. It is assumed that the pro-cognitive actions of quetiapine could be ascribed to its metabolite, nor-quetiapine, which is NRI, $5HT_{1A}$ partial agonism, $5HT_{2c}$ antagonism, $5HT_7$ antagonism and α_2 antagonism (akin to mirtazapine).

Autism Spectrum Disorder

Results are mixed regarding quetiapine efficacy for irritability associated with autism. One open-label trial[12] was positive with a mean dose of 120 mg/d. In this trial, sleep disturbance improved significantly and a

positive correlation was found between the improvements in aggression and sleep. Other 2 open-label trails were negative, though.[13–14]

(de La) Tourette Syndrome

An 8-week open label trial from Turkey[15] was positive for quetiapine efficacy in Tourette syndrome. Mean dose of quetiapine at the end of the study was 72.9 ± 22.5 mg/day.

Treatment-Resistant Juvenile Major Depressive Disorder

A case series[16] showed a favourable response to adjunctive quetiapine in TR juvenile MDD. Here, TR depression was defined as a failure to respond to a *single* adequate trial of an approved SSRI for 8-week duration. In this series, 70% qualified as responders to treatment with adjunctive quetiapine. The median dose of quetiapine was 200 mg/d.

Borderline Personality Disorder

An RCT[17] compared low vs. medium dose of quetiapine in BPD. Low dose was efficacious spanning different psychopathology domains of BPD. Participants treated with 150 mg/day of quetiapine had a significant reduction in the severity of borderline personality disorder symptoms compared with those who received placebo. 82% in the low-dosage quetiapine group were rated as responders on the clinician-rated Zanarini Rating Scale for Borderline Personality Disorder. Time to response (defined as a reduction of ⩾ 50% on Zanarini scale) was significantly shorter for both groups compared to placebo. However, Adverse events were more likely in participants taking 300 mg/day of quetiapine.

Anorexia Nervosa

A naturalistic, open-label, 12-week randomized controlled trial of low-dose (100–400 mg/day) quetiapine treatment versus treatment as usual in 33 anorexia nervosa patients has demonstrated that low-dose quetiapine treatment resulted in both psychological and physical improvements, with minimal associated side-effects.[18] Quetiapine might help as orexogenic whilst decreasing mealtime anxiety and obsessionality (cognitive inflexibility).

Obsessive-Compulsive Disorder

A single case report[19] showed a favourable response to add-on quetiapine in treatment-resistant OCD. A degree of DA blockade deems necessary to enhance serotonergic neurotransmission in the CSPTC pathway.[20] Paradoxically, quetiapine-induced OCS abound in literature.[21]

Post-Traumatic Stress Disorder

From Australia,[22] a preliminary case series of six youths (15–17 ys) in juvenile detention centre with PTSD reported an improvement in symptoms after 6 weeks of treatment with low-dose quetiapine (50–200 mg/d). Significant improvements in symptoms of dissociation, anxiety, depression, and anger were also noted over the 6-week evaluation period. Low-dose quetiapine was tolerated well, with no persisting side effects or adverse events.

Trichotillomania

We could find a single case report only from Brazil[23] where add-on quetiapine 100 mg to fluoxetine 40 mg helped a 20-year female with trichotillomania. Response was well maintained for 4 months.

Delirium

A retrospective review[24] of critically ill children with delirium, aged 2 months-20 years, showed a positive response to quetiapine, median dose 1.3 mg/kg for a median duration of 12 days. Three cases developed QT_c prolongation. These were clinically nonsignificant with no associated dysrhythmia: 2 resolved over time without intervention, and one resolved with decrease in quetiapine dosage.

Insomnia

In a Canadian survey,[25] involving 67 active child psychiatrists examined the prescription pattern for pediatric insomnia in context of depression. Melatonin (97%), trazodone (81%), and quetiapine (73%) were rated by a majority of respondents as effective.

Conclusions

This overview has casted some light on quetiapine therapreutic potential in child and adolescent psychiatry. Its pharmacological portfolio

TABLE 1

Quetiapine Uses in Child Psychiatry

INDICATION	LEVEL OF EVIDENCE*
Childhood-onset Schizophrenia**	Level I
Juvenile Bipolar Mood Disorder **	Level I
Juvenile Bipolar Depression	Level I (Negative)
Disruptive Behaviours	Level I
Autism	Level II-1
Tourette Syndrome	Level II-1
TR Juvenile MDD	Level II-3
BPD	Level I
Anorexia Nervosa	Level III
OCD	Level III
Trichotillomania	Level III
PTSD	Level II-3
Delirium	Level II-3
Insomnia	Level III

*USPSTF rankings (1998).

- Level I: Evidence obtained from at least one properly designed randomized controlled trial.
- Level II-1: Evidence obtained from well-designed controlled trials without randomization.
- Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
- Level II-3: Evidence obtained from multiple time series designs with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
- Level III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

**Only FDA Indication.

speaks to the idea of a pluripotent agent with panoply of off-label uses. Having said so, the hitherto level of evidence supporting the use of quetiapine in all these indications is highly variable (Table 1), and, hence, sound clinical acumen, manipulating all other viable treatment options at hand, would dictate its judicious and proper use and placement in real-life psychiatric practice and psychopharmacotherapy algorithms. Sound evidence supports the use of quetiapine for juvenile bipolar mania, childhood-onset schizophrenia, disruptive behavioural disorders, and borderline personality disorder. Modicum evidence supports the use of quetiapine for autism spectrum disorder, Tourette syndrome, treatment-resistant juvenile major depressive disorder, posttraumatic stress disorder, and delirium. Less compelling evidence is present for its use in anorexia nervosa, obsessive-compulsive disorder and insomnia. No evidence supports its use for juvenile bipolar depression. ✤

Disclosures

Authors declare no competing interests or financial affiliations.

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