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REVIEW ARTICLE

The Added Value of Liquid Antipsychotics: The Case of Quetiapine

Georgios Papazisis[1,*] and Spyridon Siafis[1]

[1]*Department of Clinical Pharmacology, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece*

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Abstract: ***Background*:** Antipsychotic drugs are the cornerstone of schizophrenia treatment and are also indicated for other psychotic and mood disorders. Different antipsychotic drugs and their formulations are available, though liquid forms have been overlooked.

***Methods*:** Herein the added value of liquid antipsychotics is reviewed, with a focus on the recently introduced liquid quetiapine, a frequently used antipsychotic.

***Results*:** Liquid antipsychotics are easily administrated *via* the preferable oral route, while compliance under supervised administration is transparent. Liquid forms could be preferred in patients with swallowing difficulties, which are common in elderly patients and often concealed. In this population, the availability of liquid antipsychotics could prevent errors in medication administration, which could possibly render caregivers labile to any harm caused to the patient. Aspiration, however, remains a risk with liquid formulations. Common errors in medication administration are the omission of treatment and alteration of solid oral formulations. Regarding quetiapine, omission of treatment could be associated with non-adherence as well as discontinuation symptoms, while alteration of extended release formulation could alter its pharmacokinetics. Mildly agitated and cooperative patients are another target population of liquid antipsychotics, which can induce fast sedation avoiding involuntary intramuscular injections. The combination of sedative properties and low incidence of extrapyramidal symptoms makes liquid quetiapine a valuable option for these patients, yet the current evidence is limited.

***Conclusion*:** The liquid form of quetiapine can facilitate pharmacotherapy of schizophrenia and can be defined as value added medicine bringing key benefits not only to the patients and caregivers but also to the health care system.

Keywords: Antipsychotic, quetiapine, liquid, schizophrenia, dysphagia, agitation.

1. INTRODUCTION

Antipsychotic drugs are the cornerstone of the treatment of schizophrenia and other psychotic disorders and are also indicated for bipolar disorders and as add-on treatment for major depression [1]. Successful pharmacotherapy lies in the proper selection of antipsychotic drugs and adherence to treatment. Currently available antipsychotics have distinct pharmacological properties. Selection of antipsychotic treatment is based on several factors, such as prior response or side effects, efficacy and safety profile of the drug, patient characteristics, as well as patient's preference and route of administration. Non-response or incident side effects could lead to a change of antipsychotic drugs; switching from one atypical antipsychotic to another is reported in about 30-50% of outpatients a year [2].

Compliance with treatment should be assessed before evaluating the poor efficacy of antipsychotics. Compliance (or adherence) is very challenging in chronic illness and especially in psychotic disorders. Non-compliance rates of antipsychotics vary between studies, with mean rates being about 40-50% of patients with schizophrenia, but they can be even higher. Consequences of non-compliance are relapse and persistent symptoms, as well as re-hospitalization and increased cost of treatment. Patients' preference and attitudes towards specific antipsychotic drugs must be taken into consideration when selecting an antipsychotic because they can facilitate compliance with treatment [3].

Different formulations of antipsychotics have been developed to improve clinical outcome and treatment compliance. Oral formulations are considered first-line treatment for schizophrenia. Short-acting intramuscular injections are useful in non-cooperative and agitated patients, whereas depot formulations of antipsychotics are suggested when poor compliance with oral medication is evident during maintenance treatment [4]. Rapidly dissolving tablets and liquid antipsychotics are easily administrated *via* the preferable oral route, and their compliance under supervised administration is transparent [5]. However, liquid antipsychotics have been overlooked and a small number of antipsychotics is available in liquid form [6] (Table **1**). The most recently introduced

*Address correspondence to this author at the Department of Clinical Pharmacology, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece; Tel/Fax: +30 2310 999323; ORCID: 0000-0003-1641-9095; E-mail: papazisg@auth.gr

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Table 1. Available antipsychotics with licensed oral liquid formulation. FGA: first-generation antipsychotics, SGA: second-generation antipsychotics.

Liquid Antipsychotics	
FGA	chlorpromazine, haloperidol, sulpride, trifluoperazine
SGA	amisulpride, aripiprazole, clozapine, risperidone, quetiapine

form is liquid quetiapine, which could be an important addition to the list of liquid antipsychotic drugs. Liquid antipsychotics could have unique place in pharmacotherapy, especially in patients with agitation and questioning adherence as well as with swallowing difficulties [7].

A further issue raised in the context of the current cost-constrained environment is the increasing demand for robust evidence to demonstrate the additional benefit of a new medicine *versus* the therapeutic strategy. Medicines, based on known molecules, that address healthcare needs and deliver relevant improvements for patients, healthcare professionals and/or payers are defined as value added medicines. Benefits include improved efficacy, safety and tolerability profile, better adherence, better quality of life, better convenience of use and/or patient preference' [8]. Herein, the pharmacological profile and the clinical utility of the liquid form of antipsychotics will be reviewed focusing on the added value of the recently introduced liquid quetiapine.

2. QUETIAPINE

Quetiapine is an atypical antipsychotic drug with unique pharmacodynamic and pharmacokinetic properties. The pharmacodynamic profiles of quetiapine and norquetiapine are presented in parallel (Fig. **1**), since norquetiapine is suggested to mediate some of the clinical effects of quetiapine, especially the antidepressive and anxiolytic properties [9]. Quetiapine displays moderate affinities to serotonin 5-HT_{2A} and dopamine D_2 receptors, as well as stronger affinities to histamine H_1. Norquetiapine is structurally similar to tricyclic antidepressants and it is a potent norepinephrine transporter (NET) inhibitor and 5-HT_{1A} partial agonist [9]. In addition, antagonism on muscarinic and adrenergic receptors could contribute to some of the therapeutic or side effects. Both immediate release (IR) and extended release (XR) formulations are available for quetiapine [10, 11]. Quetiapine IR displays a faster onset but shorter duration of action than quetiapine XR.

Quetiapine is approved by both Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of schizophrenia, bipolar disorder and as an augmentation treatment for major depressive disorder [10, 11]. Quetiapine is not indicated for the patients under the age of 18 years old by EMA. Though, quetiapine is approved by FDA for the treatment of schizophrenia in patients from 13 years old and bipolar mania from 10 years old [12]. Quetiapine is generally safe with common adverse event reactions being sedation, postural hypotension, metabolic disturbances (including weight gain, hyperglycemia, increased total cholesterol and triglycerides), and antimuscarinic side effects (including dry mouth and constipation). Other adverse reactions such as extrapyramidal symptoms, increased prolactin and sexual dysfunction are presented less frequently in comparison to other antipsychotics [13].

Despite these indications, quetiapine is also extensively off-label used for insomnia, generalized anxiety disorder, obsessive-compulsive disorder, psychosis associated with

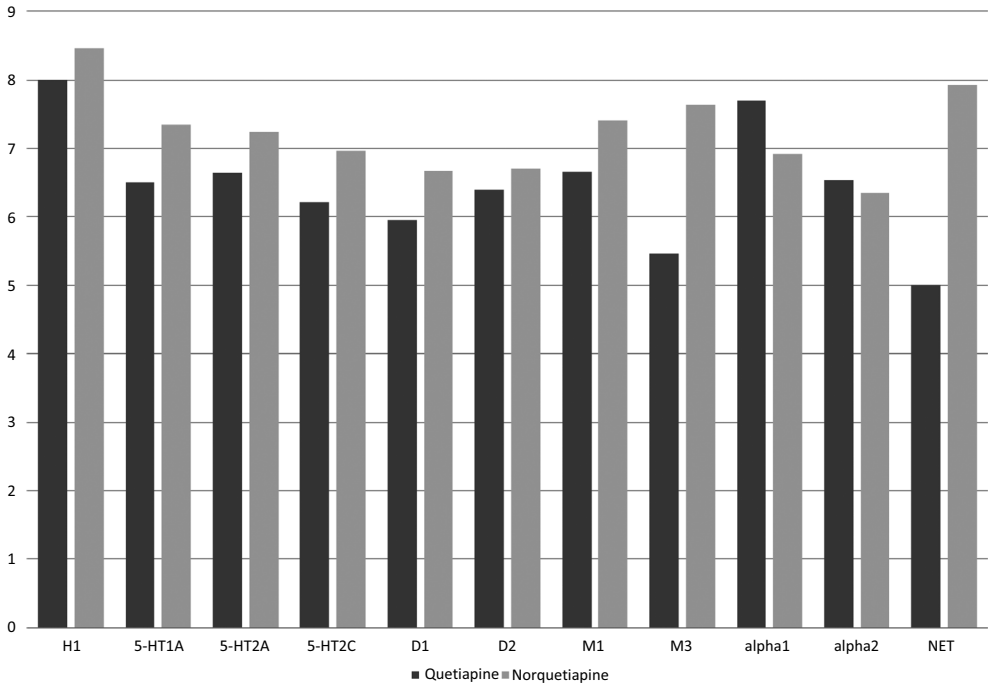

Fig. (1). Pharmacodynamic profile of quetiapine and norquetiapine. The pharmacodynamic profile on human receptors of quetiapine was extracted from PDSP database [40] and for norquetiapine from Jensen 2007 [9]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 2. Posology of liquid quetiapine. A titration phase is required during the first four days of treatment. Usual effective dose for schizophrenia and for moderate to severe manic episodes is 400-800mg (20-40ml) and for depressive episodes in bipolar disorder is up to 300mg (15 ml). For depressive episodes of bipolar disorder in individual patients could benefit by 600mg (30ml) or require a minimum dose of 200mg (10ml) due to poor tolerability [15]**.**

Indication	Range of Quetiapine Daily Dose (mg)	Equivalent ml of Liquid Quetiapine	Devise of Daily Dosage
Schizophrenia	150-750	7.5-37.5	Twice a day
Bipolar disorder			
Moderate to severe manic episodes	200-800	10-40	Twice a day
Depressive episodes	300	15	Once a day at bedtime
Maintenance treatment	300-800	15-40	Twice a day

Parkinson's disease, delirium, substance use disorders, personality disorders, as well as monotherapy for major depressive disorder. Quetiapine has also been used in dementia-related psychiatric manifestations, though antipsychotics have received a black box warning of increased mortality in dementia. The efficacy and safety of quetiapine for the above disorders are yet to be determined [14].

Besides IR and XR tablets, liquid quetiapine has recently been developed in the form of oral suspension. Quetiapine oral suspension has the indications and pharmacokinetics of quetiapine IR tablets. Each 1ml of the liquid contains 20mg of quetiapine fumarate, and different doses can be achieved depending on the indication (Table **2**) [15].

3. THE ADDED VALUE OF LIQUID ANTIPSYCHOTICS: CLINICAL UTILITY IN SPECIAL CONDITIONS AND SUBPOPULATIONS

3.1. Prevalence and Identification of Swallowing Difficulties: The Need for Proper Management

Age-related physiological changes and comorbidities can reduce swallowing capabilities in the elderly patients, as well as several diseases and drugs that could impair any of the synchronized neural and muscular mechanisms (Table **2**). According to the National Health Service (NHS), the medical term for swallowing difficulties is dysphagia, thus the terms can be used interchangeably [16]. Swallowing difficulties are suggested to be overlooked, yet with important health consequences. They are present in about one-third of patients during lifetime, and they could be more frequent in the elderly or certain settings. As a result, they range between 10-35% in patients older than 65 years old and up to 70% in nursing homes [17, 18]. Selective discomfort on swallowing pills seems to be more frequent to general swallowing problems. Tablets and capsules are intrinsically difficult to swallow due to the small size, bad taste and rigidity, which could induce discomfort and psychological aversion. A large number of patients experience discomfort swallowing tablets or capsules, while swallowing liquid or food comfortably, with a prevalence ranging among studies from 25 to 50% of patients [19].

Swallowing difficulties may raise an additional barrier to compliance with treatment, but relevant studies are lacking in patients on antipsychotic treatment. Pill characteristics such as big size, sticky tablets and bad taste seem to be common causes of swallowing discomfort and they may demotivate patients to comply with treatment [18]. A considerable number of patients with discomfort when swallowing pills are non-adherent to treatment, with about 4% of them ceasing the treatment and 10-14% delaying or missing the doses [19]. However, the rates of non-adherence may be higher due to swallowing discomfort. A prospective study in community pharmacies suggested that 23% of patients with swallowing difficulties reported intentional omission of treatment as a coping mechanism [18]. Another preliminary survey in community pharmacies reported that about 70% of the responders omitted medication due to swallowing discomfort [20].

The high prevalence of swallowing difficulties, the associated economic and health burden, as well as the increasing number of elderly populations, raise alertness for proper management of medication administration to these patients. A simple question about the presence of potential swallowing difficulties might be a good initial step. Observation of the patients during swallowing of food, liquid and/or pills would easily and reliably identify patients with swallowing difficulties. Further diagnostic investigation and etiological treatment would be the best option, yet it is limited only for certain pathological conditions [17].

3.2. Dysphagia in Schizophrenia and Antipsychotic-induced Dysphagia

Dysphagia is common in schizophrenia which affects about 23% inpatients, yet it is still poorly studied. Behavioral symptoms related to illness seem to contribute to swallowing difficulties, but antipsychotic drugs per se may impair swallowing [21]. First, drug-induced dysphagia should be excluded, since discontinuing the causative drug could improve swallowing. A recent systematic review found that both typical and atypical antipsychotics could be associated with oropharyngeal dysphagia, yet the current level of evidence is low and several confounding factors can infiltrate the association. The association with individual antipsychotics is not consistent, but haloperidol and risperidone were the most frequently typical and atypical antipsychotic associated with dysphagia respectively [22].

Antipsychotic-related dysphagia has been related to extrapyramidal symptoms (EPS) and to a lesser degree, with

disrupted salivary function and sedation. Swallowing difficulties related to EPS could be resolved with switching to a SGA with low incidence of EPS [23], such as quetiapine, olanzapine, aripiprazole and clozapine [24]. Xerostomia impairs bolus formation and it could be induced by drugs with antagonistic properties on muscarinic receptors. Moisture foods and candies to stimulate saliva production or artificial saliva could be of great help in some patients [17]. Sedative agents can inhibit the swallowing reflex by acting on the swallowing center in the brainstem. Some antipsychotic drugs have sedative properties, though they could be transient as well as could be confounded by the concomitant use of benzodiazepines or multiple sedative agents [24]. It should be noted that xerostomia and sedation can be caused by a large number of psychotropic drugs, therefore polypharmacy should be avoided.

3.3. Liquid Antipsychotics *Versus* other Coping Strategies for Swallowing Issues

Healthcare professionals should evaluate patients with swallowing difficulties and recommend appropriate management plans. When possible, etiological treatment of dysphagia must be preferred and exclusion of drug-induced dysphagia is mandatory. However, swallowing difficulties are often concealed and not reported. Patients and caregivers follow coping strategies often by their own volition, such as using facilitating techniques, omitting treatment, crushing, as well as splitting and mixing tablets with foods and liquids [19]. These strategies are usually inappropriate and potentially harmful. Licensed oral non-solid drug formulations can be a cost-effective solution when oral route administration is sufficient, otherwise, other routes of administration, *e.g*. intramuscular administration, should be used. Liquid antipsychotic may be preferable, yet studies that compare different coping strategies are lacking.

3.3.1. Omitting Antipsychotic Treatment

Omission of treatment seems to be common in nursing homes, and it might be higher in patients with swallowing difficulties (9.8% *versus* 2.9%) [25]. Besides reduced nonadherence, abrupt cessation of antipsychotics could lead to discontinuation syndromes. The symptoms of quetiapine discontinuation syndrome may include headache, nausea, vomiting, insomnia, psychosis, anxiety, irritability, and tachycardia. The IR formulations seem to be more likely to induce discontinuation syndrome in comparison to quetiapine XR [26]. Since liquid quetiapine can be more easily swallowed and masked with sweeteners, it could increase adherence rates in patients with swallowing difficulties reducing the consequences of treatment omission.

3.3.2. Altering Solid Oral Dosage Formulation

Another common coping strategy is alteration of oral solid formulations by crushing, opening, splitting and mixing pills with food or liquids. These procedures might be unlicensed and change the pharmacokinetic properties of the medication. As a result, they may be accompanied by potential harms for the patients as well as caregivers may be rendered liable to any harm caused. Consensus guidelines and audit standards suggest that manipulations of dosage form as well as mixing medicines with food should be last options and they should be used only after consideration and multidisciplinary consultations when other suitable preparations are not available [17, 27].

First of all, most of the crushing methods have limited reproducibility and poor-quality control. This could lead to under-dosage or over-dosage due to unequal splitting as well as to the loss of substance [28]. Loss of substance can be significant when crushing methods are inappropriate and can be associated with substantial economic cost [29]. In certain cases, alteration of pharmacokinetic properties might be crucial. Manipulation of extended-release pills can lead to faster absorption of the drug making patients prone to adverse events and severe intoxication, which can sometimes be fatal [19]. According to that, quetiapine XR should be swallowed as a whole and never be crushed, chewed or splitted [11]. A retrospective study of a case series suggested that acute quetiapine overdose could be associated with hypotension, tachycardia, seizures, respiratory depression, coma or even death [30]. Overdose in geriatric patients might be more dangerous due to reduced clearance rates as well as frequent comorbidities. In addition, manipulating film-coated quetiapine IR could lead to bitter taste which may demotivate patients to comply with treatment. Crushing conventional-release pills and especially when mixed with food or drink can also impair bioavailability and absorption [28].

Regarding the risk of inappropriate manipulation methods faced by the caregivers, aerosolization of substances can expose caregivers to the toxic, carcinogenic and pharmacological effects of the substance [31]. Most importantly, ethical and legal issues can be raised by manipulation of solid oral dosage formulations. Since the use of manipulated formulations is outside the licensed restrictions of a medication, it can be characterized as an off-label. Off-label use should be based on scientific evidence as well as it requires informed consent from the patients, who could be limited in geriatric patients especially with cognitive impairment and severe mental illness [28]. As a result, caregivers could be labile of any possible harmful outcome when they administer manipulated formulations in patients with swallowing difficulties.

Despite the potentially harmful consequences, manipulation of formulations is quite common, with a study about 70% of patients attending community pharmacies reporting that they crush or open pills to overcome swallowing difficulties [20]. Another survey in patients attending community pharmacies suggested that manipulation of dose was common, with crushing or cutting being the most prominent (26% of coping strategies used) followed by mixing with food or drink (13%) and opening capsules (2%). However, only 4.5% of coping strategies requested other suitable formulations [18]. Nurses or caregivers have the responsibility to administer medication in nursing homes and long-term care facilities, where elderly patients with swallowing difficulties or refusing to comply with medication are prominent. Liquid formulations are rarely available, so that medication manipulation is a common practice. A cross-sectional study suggested that about one-third of inpatients with severe mental illness receive their medication mixed with food or drink, and in some patients (10%), administration is concealed due unavailability of consent. Main reasons for manipulating and

mixing medication with food or drink were swallowing difficulties in about 62% and refusal to comply with medication in about 47% [27]. Especially in the elderly psychiatric inpatients, who commonly have swallowing difficulties, medication administration errors including inappropriate dosage manipulation are suggested to be more frequent, particularly regarding the antipsychotics dosage [25, 32, 33].

3.3.3. Liquid Versus Orodispersible Antipsychotics in Swallowing Difficulties

Both liquid and orodispersible antipsychotics can be preferred to other solid oral dosage formulations in patients with swallowing difficulties. Systematic studies that compare both formulations are lacking, but preliminary evidence can suggest that liquid antipsychotics could be more easily used. In the previous observational study about the manipulation of medication in geriatric inpatients, orodispersible tablets contained 1% of the drugs. However, they were misused and still crushed with consequently possible modification of the efficacy [32]. In another observational study in care home residents with swallowing difficulties, caregivers prepared orodispersible tablets according to the instructions of the capsule formulations of the medication [25]. As a result, orodispersible tablets can be wrongly used as conventional pills, possibly due to lack of training of caregivers and patients. Orodispersible tablets seem to facilitate swallowing and be more acceptable than other solid formulations in patients with dysphagia [34], yet oropharyngeal residues as well as airway compromise did not differ between orodispersible and conventional tablets [35]. However, liquid formulations, especially thin liquids, might be associated with an increased risk of aspiration and aspiration-induced pneumonia. Proper volume of liquid, increased viscosity as well as proper swallowing techniques could reduce the risk of aspiration [36]. Medication administration errors can also accompany the use of liquid formulations, especially crude estimation of volume could result in inaccurate doses. Administration and preparation of liquid formulations should be performed according to the summary of product characteristics and all related information should be included in the patient information leaflet. As a result, liquid formulations could be an attractive alternative to oral solid formulations, but the risk of aspiration as well as potential administration errors should be considered and evaluated.

3.4. Emergency Setting: Agitated Patients with Schizophrenia or Bipolar Disorder

Episodes of agitation and aggression are frequently presented in about 90% of patients with schizophrenia or bipolar disorder during their lifetime, and they require proper and prompt treatment [37]. Expert consensus recommendations suggest that goals of treatment of agitation are to stabilize the patient, avoid possible restrictive settings, as well as to ensure the physician-patient relationship and arrange an after-care plan. In this setting, the agitated patients should be rapidly calmed without over-sedation and they should be involved in selecting both the drug and route of administration. In addition, oral administration, especially of dispensable tablets and solutions/suspensions should be preferred to intramuscular injections in mildly agitated patients [38].

A recent systematic review of RCT could not identify consistent superiority of any pharmacological interventions for agitation related to schizophrenia and bipolar disorder. The identified literature involved olanzapine, aripiprazole, haloperidol, risperidone, ziprasidone and lorazepam, mostly administrated *via* parenteral routes [37]. Short-acting intramuscular antipsychotics should be used mostly in emergency settings and when the patients are not cooperative. Parenteral administration of antipsychotics could disintegrate the therapeutic alliance with the patient, since they are invasive, painful and often involuntary administrated [7]. Other formulations, such as liquid antipsychotics, might be preferred in cooperative and less agitated patients. Liquid antipsychotics are more easily administrated, have a fast onset of action and secure compliance in comparison to tablets, as well as they might be preferred by patients and strengthen the physician-patients' relationship. Despite the limited clinical evidence, liquid antipsychotics seem to be efficacious and tolerable as the tablet and intramuscular formulations [4].

Liquid quetiapine could be a reasonable choice for mildly agitated patients. In a short-term liquid, quetiapine could stabilize agitated patients with its combined antipsychotic and sedative properties. The efficacy and tolerability of quetiapine, including the liquid formulation, have not been studied extensively in patients with agitation. Clinical trials suggest that quetiapine is superior to placebo and does not differ significantly to haloperidol for aggression and agitation in patients with psychosis [38]. In long-term, liquid quetiapine can improve adherence to treatment. Liquid quetiapine could be selected by mildly agitated patients willing to cooperate. It can secure compliance with treatment under supervision, avoiding unnecessary and involuntary administration of intramuscular injections. Along with the reduced risk for extrapyramidal symptoms, these will improve patients' perceptions and attitudes towards the treatment, making them more willing to comply with maintenance treatment. Since SGA are preferred during maintenance treatment, liquid quetiapine or its other formulations could be continued during maintenance treatment avoiding unnecessary switching of antipsychotics.

CONCLUSION

Liquid quetiapine has the same efficacy and safety profile with immediate release oral form of quetiapine. Consequently, it can be used for the same indications (schizophrenia, bipolar disorder). Our review suggests that the liquid form of quetiapine has significant clinical utility in patients with poor adherence, in emergency settings as well as in patients with swallowing difficulties, thus, it can be defined as value added medicine. Value-added medicines represent an opportunity for increasing the cost-effectiveness of treatments or services that may bring substantial value to individual patients and society. They may also represent an opportunity to limit therapeutic escalation by increasing the number of treatment options and to reduce budget impact by creating an intermediate step before switching to more costly products. Additionally, they offer the opportunity to tailor and expand access of well-known therapies to particular patient subgroups' needs, such as vulnerable patients or patients requiring frequent dosing adjustments [39]. The liquid

quetiapine form has added value for the patients delivered by the convenience of use and its use in specific subpopulation with high unmet needs (dysphagia/swallowing difficulties). These improvements may enhance adherence, health outcomes or quality of life, and match patients' and/or caregivers' preferences. However, the risk of aspiration and potential administration errors cannot be excluded and should always be considered with the use of liquid formulations [40].

Concluding, the liquid form of quetiapine can be defined as value added medicine bringing key benefits to the patients, the caregivers and also to the health care system. Since value-added medicines may contribute to favorably impact healthcare budgets and bring substantial value to individual patients and the society, the liquid form of quetiapine should be implemented in routine clinical practice.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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