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# Health-related quality of life and functioning in bipolar disorder: the impact of pharmacotherapy

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Bipolar disorder has a major deleterious impact on many aspects of a patient's functioning and health-related quality of life. Although the formal measurement of these deficits has been neglected until recently, many well-designed trials now include an assessment of functioning and health-related quality of life using one or more rating scales. This review describes recent developments in the measurement of functioning and health-related quality of life in bipolar disorder, and discusses the evidence that medications that improve symptoms in bipolar disorder also offer clinically relevant benefits in functioning and health-related quality of life. Direct comparisons of the benefits of medications including atypical antipsychotics are problematic due to differences in trial populations, study durations and rating scales. Data from quetiapine trials indicate that this medication offers prompt and sustained improvement of functioning in patients with mania and enhancement of health-related quality of life in patients with bipolar depression, to accompany the significant improvements in mood episodes.

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Bipolar disorder is a chronic, episodic condition characterized by dramatic and largely unpredictable changes in mood, energy and ability to function. Although estimates vary, the lifetime prevalence of bipolar disorder may be up to 3.9% of the adult population [1]. In global terms, over 28 million adults were estimated to be living with bipolar disorder in 2002 [101]. Due to the nature of the illness, the lives of many others such as family members and carers are also profoundly affected.

Mood in bipolar disorder may swing from euphoria and/or extreme irritability (defined as 'mania') to depressed mood or loss of interest or pleasure ('bipolar depression'). These mood swings are typically experienced repeatedly throughout a patient's life. For many patients, the episodes of extreme mood are interspersed by apparently symptom-free periods ('euthymia'), although careful investigation shows that over a third of patients continue to experience residual symptoms during these periods [2]. Acute episodes may vary in duration as well intensity over time [3]. Early in the

course of the disease, for example, the periods between acute episodes may last months or even years, but later these symptom-free periods tend to decrease [4].

Bipolar disorder may be divided into two major subtypes: 'bipolar I' and 'bipolar II'. Establishing a diagnosis of bipolar I disorder requires a history of at least one manic episode, with or without depressive symptoms. A diagnosis of bipolar II disorder requires the presence of both depressive symptoms and a less severe form of mania ('hypomania'). Patients with bipolar II disorder may spend more than 50% of their time in a depressed state [5]. Bipolar II disorder, in particular, has been under-recognized until recently, in part owing to difficulties in distinguishing bipolar from unipolar depression.

A consequence of the symptoms of bipolar disorder is that patients experience a debilitating decrease in functioning. Typically they have difficulty in maintaining long-term relationships and they perform poorly at school or work, which impacts on opportunities for

Table 1. Generic HRQoL measures used in patients with bipolar disorder .

| Name | Key features | Patient population | Key findings | Ref. |
|------|-------------|-------------------|-------------|------|
| **Physician-based assessment** | | | | |
| GAF/GAS | Physician assessment of psychological, social and occupational functioning | Bipolar manic patients versus patients with unipolar depression | Patients with BD had more severe work impairment than those with unipolar depression | [51] |
| | | Euthymic BD patients | Number of prior episodes predicts poorer functioning<br>Number of prior depressive episodes was a stronger determinant of poor outcome than number of prior manic episodes | [43] |
| QoLI | Interview-based tool examining: health and functioning, socioeconomics, psychological/spiritual wellness and family life | Manic versus depressed patients with BD | BD–depressed patients reported poorer HRQoL than BD–manic patients | [41] |
| **Self-reported assessment** | | | | |
| EUROQoL | Self-assessment using five questions on mobility, self-care, usual activities, pain/discomfort and anxiety/depression, and a 100-point visual analog scale ranging from worst possible to best possible health state on the current day | Patients with BD: manic, hypomanic, depressed, mixed or euthymic | Significant differences in HRQoL across mood states<br>Patients in mixed or depressed states scored lower than those in manic/hypomanic or euthymic states | [42] |
| SF-36 | Eight subscales:<br>physical functioning,<br>social functioning,<br>sole limitations (physical),<br>role limitations (emotional),<br>pain, mental health,<br>general health and<br>vitality | Euthymic and depressed patients with BD | Valid and reliable tool for the assessment of HRQoL among BD patients sensitive to changes in symptoms (particularly depression) over time | [34] |
| | | Patients with BD type I and NOS | Patients with BD reported poorer quality of life than patients with a range of other mental disorders | [32] |
| | | Patients with BD versus patients with chronic back pain and general population sample | BD associated with substantial impairment compared with the general population | [31] |
| | | Patients with BD type I currently/most recently depressed | Patients with BD scored consistently lower than published data for patients with unipolar depression for general health, social functioning, role-physical and role-emotional | [33] |
| PGWB | Consists of 22 items with 6-point response scales representing intensity/frequency<br>Assesses anxiety, depression, HRQoL, positive wellbeing, vitality, general health and self-control | Patients with BD who were symptom-free | Patients with low HRQoL scores were more likely to experience a depressive relapse in the subsequent 4 weeks | [71] |
| QLDS | 34-item scale designed to evaluate the extent to which the patient feels their needs are satisfied | Euthymic and depressed patients with BD | Valid and reliable tool for the assessment of HRQoL among BD patients sensitive to changes in symptoms (particularly depression) over time | [34] |

BD: Bipolar disorder; BD type I: diagnosis requires a history of at least one manic episode, with or without depressive symptoms; BD type II: diagnosis requires the presence of both depressive symptoms and a less severe form of mania ('hypomania'). EUROQoL: European Quality of Life Interview; GAF/GAS: Global Assessment of Functioning/Global Assessment Scale; HRQoL: Health-related quality of life; NOS: Not otherwise specified; PGWB: Psychological General Well-Being; QLDS: Quality of Life in Depression Scale; Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire; QoLI: Quality of Life Interview; SDS: Sheehan Disability Scale; SF-36: Medical Outcomes Study 36-item Short-Form Inventory; WHO-QoL-BREF: World Health Organization Quality of Life Assessment.

Table 1. Generic HRQoL measures used in patients with bipolar disorder (cont.).

| Name | Key features | Patient population | Key findings | Ref. |
|---|---|---|---|---|
| Q-LES-Q | Assesses degree of satisfaction with physical health, mood, family relationships and daily functioning in the preceding week | Patients with BD in remission versus patients with schizophrenia and controls | Euthymic BD patients had better functioning than did those with schizophrenia and comparable scores to those of healthy controls | [46] |
| | | Patients with BD defined as interepisode | Patients with lower depression scores had lower HRQoL scores | [36] |
| | | Patients with BD type I, II or NOS | BD patients with a younger age of onset had poorer HRQoL | [72] |
| | | Patients with BD manic, depressed or mixed | BD–depressed patients reported poorer HRQoL than BD–manic patients | [44] |
| SDS | Assesses work, family and social functioning during the preceding month using self-rated 10-point Likert response scales | Mixed sample of patients including a small number with BD | Patients with BD were more likely to report lower HRQoL and loss of work time | [73] |
| | | Patients with BD versus community control group | Patients with BD reported significantly greater impairment in work-related performance, social/leisure activities and social/family interactions compared with normal controls | [38] |
| | | Patients with BD manic or depressed | Patients with BD who reported depressive symptoms in the preceding 4 weeks reported significantly greater impairment in work-related performance, social/leisure activities and social/family interactions compared with those reporting manic symptoms | [39] |
| WHO-QoL-BREF | Assesses satisfaction with physical and psychological functioning, social relationships and environment using self-rated 5-point Likert response scales | Patients with BD in remission versus patients with schizophrenia and controls | Euthymic BD patients reported better HRQoL than those with schizophrenia, comparable with controls | [46] |
| | | Outpatients with BD type I or II | Majority of patients reported fair/average HRQoL | [74] |
| | | Euthymic BD patients and those with comorbid substance abuse disorder | BD patients with comorbid substance abuse disorder reported poorer HRQoL than BD patients with no comorbidity Patients with more severe alcohol dependence reported the poorest HRQoL | [26] |

BD: Bipolar disorder; BD type I: diagnosis requires a history of at least one manic episode, with or without depressive symptoms; BD type II: diagnosis requires the presence of both depressive symptoms and a less severe form of mania ('hypomania'). EUROQoL: European Quality of Life Interview; GAF/GAS: Global Assessment of Functioning/Global Assessment Scale; HRQoL: Health-related quality of life; NOS: Not otherwise specified; PGWB: Psychological General Well-Being; QLDS: Quality of Life in Depression Scale; Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire; QoLI: Quality of Life Interview; SDS: Sheehan Disability Scale; SF-36: Medical Outcomes Study 36-item Short-Form Inventory; WHO-QoL-BREF: World Health Organization Quality of Life Assessment.

employment and finances. They are also at a substantially increased risk of suicide, particularly during depressive episodes. As such, bipolar disorder has a wide-ranging impact on a patient's perception of his or her health-related quality of life (HRQoL), which captures the sum of physical, psychological (emotional and cognitive and social functioning.

Observations on functioning in bipolar disorder
Despite the importance of impairments in functioning and HRQoL for patients with bipolar disorder, these deficits have until recently been under investigated.

Educational achievement, employment opportunities, finances and interpersonal relationships are all typically impaired in patients with bipolar disorder [6,7]. These impairments also tend to increase with time. For example, Coryell and colleagues measured psychosocial functioning in patients with bipolar depression at the initiation of treatment and again 5 years later [8]. Although patients initially had comparable functioning to their matched relatives, at 5 years they demonstrated profound impairments across all functional domains. They were less likely to be employed or married and, if they had been married, were more likely to be divorced [8]. Other studies confirm the adverse consequences of bipolar disorder for functioning and satisfaction with life. Abood and colleagues, for example, identified greater rates of hospital admissions and more frequent residential moves compared with other psychiatric patients [9], while Hirschfeld and colleagues stressed the long-term consequences for careers, especially from

Table 2. Pharmacotherapy outcomes studies evaluating HRQoL among patients with bipolar disorder—manic episode.

| Comparators | Patient population | Study duration | HRQoL instrument | Key findings | Ref. |
|---|---|---|---|---|---|
| **Quetiapine** | | | | | |
| Quetiapine added to lithium or divalproex | Acute mania n = 191 | 3 weeks | GAS | Addition of quetiapine resulted in greater improvement in GAS scores, although the difference did not reach statistical significance | [55] |
| Quetiapine versus placebo added to lithium or divalproex (pooled data from two studies) | Acute mania n = 402 | 3 or 6 weeks | GAS | Addition of quetiapine resulted in significantly greater improvement in mean GAS score (p < 0.05) | [56] |
| Quetiapine versus lithium versus placebo | Acute mania n = 302 | 12 weeks | GAS | Significant improvement in GAS scores versus placebo (p < 0.001) after 3 weeks. Continued improvement and separation from placebo at 12 weeks (p < 0.001) | [52] |
| Quetiapine versus haloperidol versus placebo | Acute mania n = 302 | 12 weeks | GAS | Significant improvement in GAS scores versus placebo (p < 0.05) after 3 weeks. Continued improvement and separation from placebo at 12 weeks (p < 0.001) | [53] |
| Quetiapine versus placebo (pooled data from above two monotherapy studies) | Acute mania n = 403 | 12 weeks | GAS | Significant improvement in GAS scores versus placebo (p < 0.001) after 3 weeks. Continued improvement and separation from placebo at 12 weeks (p < 0.001) | [54] |
| **Olanzapine** | | | | | |
| Olanzapine versus placebo | Mania or mixed n = 139 | 3 weeks followed by 49-week extension | SF-36 | Olanzapine associated with significantly greater improvements in physical functioning only during acute therapy. Significant benefit for olanzapine for bodily pain, vitality, general health, role–emotional and social functioning emerged during the extension phase | [59] |
| Olanzapine versus haloperidol | Acute mania n = 453 | 6 weeks plus 6 weeks continuation | SF-36 | Olanzapine associated with significantly greater improvements in HRQoL versus haloperidol | [58] |
| Olanzapine versus divalproex | Acute mania n = 120 | 12 weeks | Q-LES-Q | Comparable improvements in HRQoL between olanzapine and divalproex | [60] |
| Olanzapine added to lithium or valproic acid | Manic or mixed n = 336 | 6 weeks | QOLI | Addition of olanzapine associated with significantly greater improvements in HRQoL compared with lithium or valproic acid alone | [61] |
| **Risperidone** | | | | | |
| Risperidone versus placebo | Acute mania n = 283 | 3 weeks then 9-week extension | GAS | Risperidone associated with greater improvements in functioning versus placebo | [62] |
| **Ziprasidone** | | | | | |
| Ziprasidone versus placebo | Acute mania n = 210 | 3 weeks | GAF | Ziprasidone associated with significantly greater improvements in functioning versus placebo | [63] |

GAF: Global Assessment of Functioning; GAS: Global Assessment Scale; HRQoL: Health-related quality of life; Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire; QoLI: Quality of Life Interview; SF-36: Medical Outcomes Study 36-Item Short-Form Inventory.

an early disease onset [6]. An increased history of criminality may accompany the manic symptoms of bipolar disorder [10]. Men with co-occurring substance abuse appear to be at a particularly elevated risk [11].

Psychosocial functioning may be reduced even during apparently symptom-free periods. Why this should be so is not fully resolved, but the presence of a chronic cognitive impairment characteristic of bipolar disorder may be a contributory
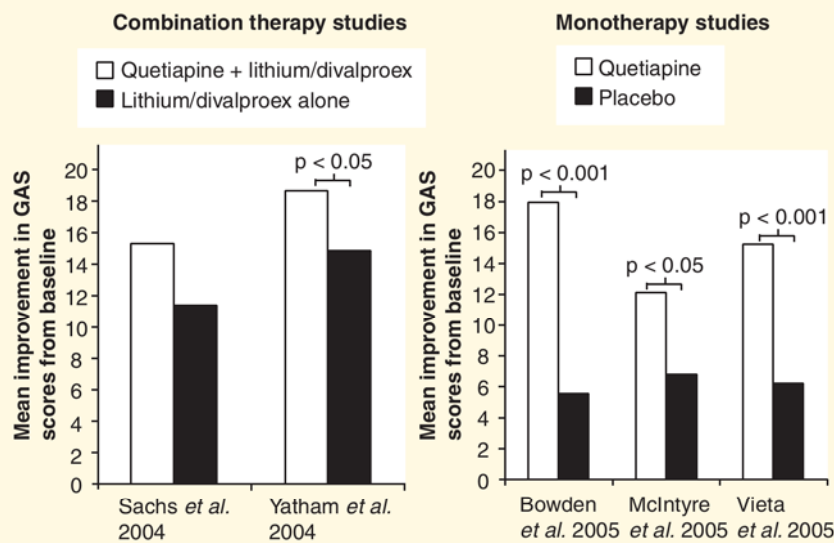
Figure 1. Improvement in functioning assessed using the GAS over the first 3 weeks of quetiapine combination or monotherapy for acute bipolar mania. GAS: Global Assessment Scale. Adapted from [52,53,55,56].

factor [12,13]. Functioning has been reported to be reduced early in the course of bipolar disorder, as early as after the first manic episode [14].

### Effects of comorbidity

It is a common clinical observation that patients with bipolar disorder display medical and psychiatric comorbidities [15–16]. The Epidemiologic Catchment Area study confirmed this by finding that 46% of patients with bipolar disorder abused or were dependent on alcohol, 41% abused or were dependent on drugs, 21% had comorbid panic disorder and 21% had comorbid obsessive-compulsive disorder [17–19].

Other psychiatric illnesses frequently co-occurring with bipolar disorder include anxiety, post-traumatic stress disorder and attention-deficit/ hyperactivity disorder (ADHD) [20–22]. Comorbid anxiety occurs in approximately half of patients with bipolar disorder at some point during their lifetime, while experiences of post-traumatic stress disorder may be almost universal [23]. ADHD and bipolar disorder co-occur in a substantial proportion of primarily pediatric patients. Distinguishing ADHD and the manic symptoms of bipolar disorder may be problematic and estimates of the concurrence rates vary with the diagnostic criteria adopted.

These comorbidities cause a substantial additional burden to that experienced by the patient with bipolar disorder [24]. Drug abuse, for example, impairs functioning to such an extent that it doubles the risk of suicide in patients with bipolar disorder, a group that is already at high risk compared with the general population [25,26].

Besides decreasing functioning, comorbidities also have the potential to complicate the diagnosis and the response to treatment.

### HRQoL studies in bipolar disorder

Despite observational evidence for the devastating impact of bipolar disorder on HRQoL, until recently, there has been limited formal research that quantifies this impairment and even less that quantifies the impact of treatment.

### HRQoL instruments

There is currently no validated, disease-specific instrument for measuring HRQoL in bipolar disorder reported in the scientific literature, although evaluations of potential tools are under way (e.g., McLeod and colleagues 2005 [27]). However, there are a range of generic rating scales that have proved informative in exploring the impact of bipolar disorder on HRQoL. The generic nature of these instruments has permitted comparisons of bipolar disorder with other medical and psychiatric conditions (TABLE 1). Unfortunately, the lack of consensus on which instruments may be optimal has meant there has been little standardization across trials of bipolar disorder.

### Self-reported assessments

Many of the instruments listed in TABLE 1 are based on self-evaluation by the patient. Self-evaluation has the advantage of revealing patients' insights without being filtered through the clinician's perspective, but has the disadvantage that the psychopathology itself may distort how individuals perceive their HRQoL. For bipolar disorder, the patient's elevated mood state is likely to affect HRQoL perception, and depressed mood in particular may cause patients to express greater dissatisfaction with their social functioning [28,29]. As a consequence, medications that offer mood stabilizing effects are likely also to impact substantially on measures of HRQoL.

Probably the most widely used self-evaluation tool for measuring HRQoL in general psychiatric illnesses has been the Medical Outcomes Study 36-Item Short Form Inventory (SF-36) [30]. The SF-36 contains eight subscales that assess physical and social functioning, role limitations (physical and emotional), pain, mental and general health, and vitality. The overall domain score ranges from 0 (worst possible health) to 100 (best possible health). Patients with bipolar disorder report reduced SF-36 subscale scores compared with the general population, patients with other mental illness and those with unipolar depression [31–33].

The SF-36 was used in one of the largest studies of bipolar depression performed to date [33]. This reported low scores on social functioning (score 29.9), role–physical (36.7), role–emotional (11.4), mental health (31.0) and vitality (22.4). Another large study observed that depressive symptoms were predictive of lower SF-36 scores in the mental health and physical domains, as
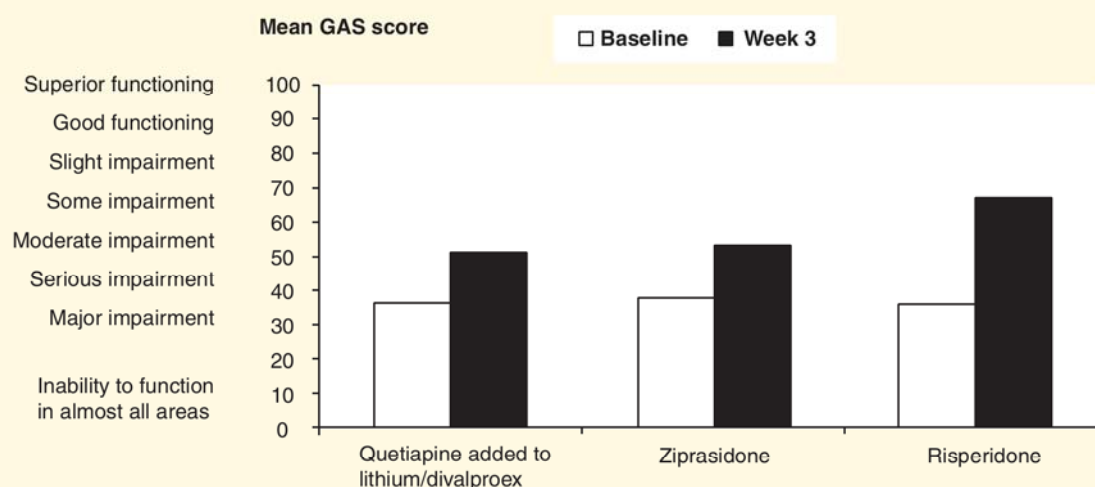
Figure 2. Comparative improvement in functioning as assessed using the GAS/GAF during the first 3 weeks of treatment with quetiapine, ziprasidone and risperidone. GAF: Global Assessment of Functioning; GAS: Global Assessment Scale. Adapted from [55,62,63].

well as the overall Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) score [24]. All subscale scores in the Yatham study correlated negatively with Hamilton Rating Scale for Depression (HAM-D) scores, confirming that a greater severity of depression is associated with an increased impairment of HRQoL.

Again confirming clinical impression, a study of patients with bipolar I disorder observed that SF-36 subscale scores for physical functioning, role–physical, role–emotional, mental health, and vitality were lower for patients in a depressed than a euthymic episode [34]. In contrast to previous studies, however, these authors observed only modest test–retest reliability for the SF-36, with intraclass correlations over an 8-week period ranging from 0.18 (role–emotional) to 0.80 (physical functioning) for euthymic patients.

A second instrument, which is increasingly used in bipolar disorder trials, is the Q-LES-Q [35]. The Q-LES-Q includes eight subscales that measure physical health, mood, leisure time activities, social relationships, general activities, work, household duties and school/coursework, with scores ranging from 0 to 100. The Q-LES-Q was developed for use in depressed patients but offers high internal consistency, test–retest reliability and validity for patients with a range of psychiatric illnesses. Intraclass coefficients of reliability ranged from 0.63 (leisure time activities) to 0.89 (school/course work) for patients with major depressive disorder, according to the originators [35]. The Q-LES-Q is also sensitive to changes with treatment.

In a study of patients who were not currently experiencing symptoms of bipolar disorder, Q-LES-Q scores were 35–39% [36], which suggests more severe disease than

reported in outpatients with major depression (42%) or seasonal affective disorder (44%), as well as the general population (83%) [37]. The Q-LES-Q correlates negatively with HAM-D and Clinical Global Impressions-Improvement (CGI-I) scores.

The Sheehan Disability Scale (SDS) is a self-rated instrument that has been utilized to assess functional impairment in a range of mental health disorders by aggregating scores for three domains: work and school, social life, and family life. Scores are reported on a 10-point Likert scale, where 10 indicates an inability to perform any activity. The SDS has been adopted in a number of studies of bipolar disorder [38,39], including the recently completed confirmatory trial of the efficacy of quetiapine in bipolar depression [40].

Other self-report tools have been used less frequently in published trials of bipolar disorder, as shown in TABLE 2.

Physician-based assessments

Physician-based instruments for assessing functionality have also proven to be informative. These have included the Global Assessment Scale (GAS) and the related Global Assessment of Functioning Scale (GAF), which offer a broader definition of functioning than the SF-36 and Q-LES-Q by encompassing psychological, social and occupational functioning. Scores on the GAS and GAF range from 1 (sickest) to 100 (healthiest), and both GAS and GAF demonstrate good reliability for a range of patient populations.

The Quality of Life Interview (QOLI) is a physician-based interview to assess patients with a range of psychiatric illnesses, including bipolar disorder [41]. It potentially has greater value in depressive than manic episodes. The QOLI consists of a
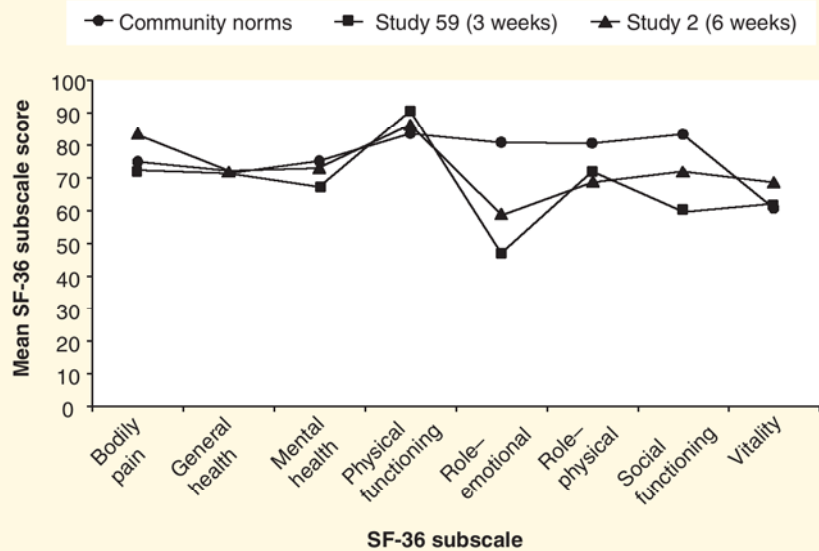
Figure 3. Improvement in HRQoL assessed using the SF-36 after 3 and 6 weeks' treatment with olanzapine compared with published community norms. SF-36: 36-Item Short Form Inventory. Adapted from [58,59].

multiple domains of functionality and HRQoL. These data typically derive from well-designed trials in acute mania and acute bipolar depression.

As described previously, mood alters self-perception and has a confounding effect on self-assessment instruments such as the SF-36 and Q-LES-Q. In addition, rating scales for assessing mood, such as the Young Mania Rating Scale (YMRS), the Montgomery–Asberg Depression Rating Scale (MADRS), the HAM-D and the Hamilton Rating Scale for Anxiety (HAM-A) share items also measured on HRQoL scales. It can therefore be appreciated that the medication-induced improvements observed in HRQoL may be explained in part by improvements in mood, and that distinguishing direct from indirect effects on HRQoL is problematic.

153-item scale for measuring global life satisfaction and quality of life in eight domains: living situation, daily activities and functioning, family relations, social relations, finances, work and school, legal and safety issues, and health.

### Assessing the impact of bipolar episodes on HRQoL
Studies that have assessed HRQoL in bipolar disorder are summarized in TABLE 1. These show a consistent pattern of significant and pervasive impact of the illness on HRQoL. HRQoL is affected across all mood states, even in periods of apparent euthymia, and the impact is greatest from depressive rather than manic symptoms [24,33,39,41–44].

### HRQoL in bipolar disorder versus other medical & psychiatric illnesses
HRQoL instruments reveal that the burden of bipolar disorder is at least equivalent to chronic medical illnesses such as osteoarthritis, diabetes and asthma [31,38,45–49].

Compared with other chronic psychiatric illnesses, bipolar disorder is associated with greater decrements in HRQoL than unipolar depression and schizophrenia [33,45,50–51].

### Effects of pharmacotherapy on HRQoL
Observations in clinical practice may suggest that improvements in symptoms with therapy are accompanied by improvements in functionality and HRQoL in bipolar disorder. Historically, there are limited trial data to confirm the benefits of pharmacotherapy for HRQoL, or the correlation of symptom improvement with improvement in HRQoL. However, data are now emerging, particularly for the newer atypical antipsychotics, to indicate that treatment does benefit

### HRQoL outcomes in acute mania studies
Measures of functioning such as the GAF or GAS have been included as a secondary end point in a number of clinical studies that explored the efficacy and tolerability of atypical antipsychotics, including quetiapine, risperidone and ziprasidone. By contrast, SF-36, Q-LES-Q and QOLI were the instruments of choice in the olanzapine mania studies (TABLE 2).

### Quetiapine
Quetiapine has demonstrated efficacy both as monotherapy and as combination therapy with lithium or divalproex for the treatment of acute manic episodes of bipolar I disorder. Reductions in mean YMRS score, the primary end points in these studies, were significantly greater for quetiapine monotherapy compared with placebo [52–54], and for adjunctive therapy including quetiapine compared with placebo added to lithium or divalproex [55,56]. Effect size calculations for the pooled monotherapy data confirm the clinical benefit of quetiapine compared with placebo, as the calculated value of 0.68 falls within the limits for a moderately sized clinical effect (0.40–0.79) [54,57]. Quetiapine was well-tolerated, with the most common adverse events with monotherapy being mild-to-moderate somnolence and dry mouth. Levels of extrapyramidal symptoms or emergent depression were similar for quetiapine and placebo in each of the mania studies.

Measurement of GAS in these studies demonstrated a significant improvement in functioning associated with quetiapine therapy. This was achieved by 3 weeks (the first assessment of HRQoL after treatment initiation) both with quetiapine monotherapy and with quetiapine as adjunct to lithium or divalproex (FIGURE 1) [52–53,55]. In a pooled analysis of the two monotherapy studies, quetiapine treatment

Table 3. Pharmacotherapy outcomes studies evaluating HRQoL among patients with bipolar disorder-depressive episode.

| Comparators | Patient population | Study design | HRQoL instrument | Key findings | Ref. |
|---|---|---|---|---|---|
| Quetiapine versus placebo | Bipolar I or II depression n = 442 | 8 weeks, randomized, double-blind | Q-LES-Q* | Quetiapine monotherapy is associated with significant improvement in HRQoL compared with placebo (p < 0.001) Greater improvement in severity of illness associated with greater improvement in HRQoL | [65] |
| Olanzapine versus olanzapine–fluoxetine combination | Bipolar I depression n = 833 | 8 weeks | SF-36 | Olanzapine monotherapy is not associated with significantly greater improvement in HRQoL versus placebo Olanzapine/fluoxetine combination associated with significantly greater improvement in HRQoL versus olanzapine monotherapy and placebo | [67] |

*Short form.
Bipolar I: diagnosis requires a history of at least one manic episode, with or without depressive symptoms; Bipolar type II: diagnosis requires the presence of both depressive symptoms and a less severe form of mania ('hypomania'); HRQoL: Health-related quality of life; Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire; SF-36: Medical Outcomes Study 36-Item Short-Form Inventory.

produced an additional, significant 9-point improvement from baseline at 3 weeks compared with placebo [54]. Importantly, the improvements in GAS score associated with quetiapine therapy continued to increase over the following 9 weeks, providing a significant 14-point improvement over placebo at study end [52–53]. In a pooled analysis of the two combination therapy studies, quetiapine added to lithium or divalproex achieved an approximately 4-point improvement in score at 3 weeks compared with lithium or divalproex alone (p < 0.05) [56].

Olanzapine

The effect of olanzapine on HRQoL in patients with acute mania or mixed mood episodes has been reported in three studies of olanzapine as monotherapy and in one study of olanzapine added to lithium or valproic acid (a medication related to divalproex) (TABLE 2) [58–61].

In a study using the SF-36, the only statistically significant benefit for olanzapine therapy over placebo during the 3-week acute phase of the study was improvement in physical functioning [59]. In addition, benefits for active treatment were observed on bodily pain, vitality, general health, role–emotional and social functioning; these emerged later during the 49-week extension phase [59]. This suggests that some of the benefits of olanzapine on HRQoL may require treatment over several weeks before emerging.

Shi and colleagues, also using the SF-36, reported that olanzapine monotherapy offered overall improvements in HRQoL comparable to haloperidol [58]. Scores for individual dimensions showed a complex pattern of change at the 6- and 12-week assessments. Modest changes were reported for olanzapine at the 6-week assessment, with greatest improvements in role–emotional and social functioning, but a worsening of scores for general health and vitality. Patients treated with haloperidol reported a worsening in five of the eight domains

including general and mental health, physical functioning, role–physical and vitality. At the 12-week assessment, olanzapine-treated patients reported marked improvements in seven of the eight domains, three significantly superior to haloperidol. Again, these findings may suggest a delay of several weeks before the full benefit of olanzapine therapy on HRQoL emerges.

Revicki and coworkers used the Q-LES-Q to compare the effects of olanzapine and divalproex on HRQoL at 6 and 12 weeks after discharge from hospital [60]. They found that olanzapine and divalproex offered comparable improvements across Q-LES-Q subscales at both assessments.

Finally, in a study in which olanzapine was added to lithium or valproic acid, Namjoshi and coworkers demonstrated significant improvements in life satisfaction based on the QoL in patients receiving adjunctive therapy [61].

Ziprasidone

In a 3-week study of the efficacy of ziprasidone monotherapy in the treatment of acute bipolar mania, ziprasidone-treated patients achieved a 15-point improvement in their mean GAF scores, compared with an 8-point improvement for patients treated with placebo (p < 0.005). Significant separation between the treatment groups was evident by the first week of treatment and was maintained throughout the study.

Risperidone

Recently, Hirschfeld and colleagues examined changes in functionality based on the GAS during a 9-week follow-up of patients who participated in 3-week placebo-controlled trials of risperidone therapy in acute bipolar mania [62]. After initial randomization to risperidone or placebo, patients received open-label risperidone therapy. Mean GAS scores improved significantly in both groups during the 3-week placebo-controlled phase, with a greater improvement in the risperidone than
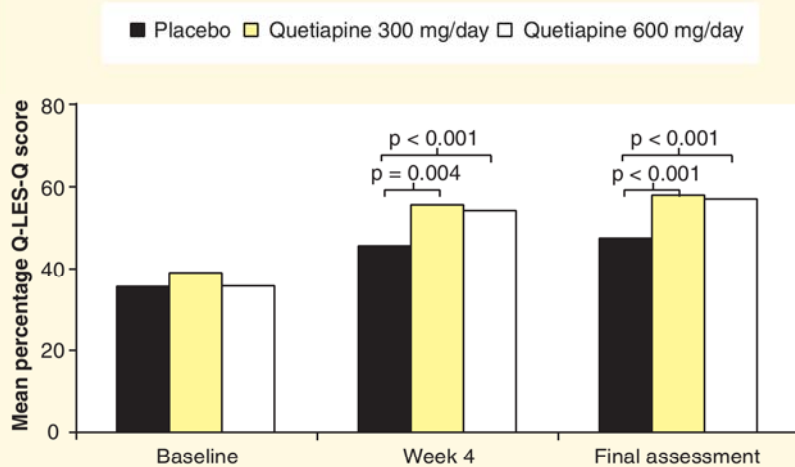
Figure 4. Improvement in HRQoL assessed using the Q-LES-Q short form during 8 weeks of treatment with quetiapine (300 or 600 mg/day) or placebo among adult patients with bipolar I or II depression. HRQoL: Health-related quality of life; Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire. Adapted from [5].

placebo group (mean changes 41.9 and 30.1, respectively), and these improvements continued with 9-week open-label risperidone (mean changes 10.6 and 10.8, in the respective groups) [62].

### Comparing the effects of atypical antipsychotics on HRQoL in bipolar mania

Based on the currently available data, described previously, it is not possible to directly compare antipsychotic agents for their ability to improve functionality and HRQoL during treatment for acute mania. Differences in study design (including study populations and durations of treatment) and in assessment instruments preclude cross-study analyses, although limited comparisons may be possible in the studies that used the GAS.

Analysis of absolute GAS score changes in one quetiapine study shows that addition of quetiapine to ongoing lithium or divalproex improved patient functioning from a mean of 36.0 points (representing major functional impairment) to 51.32 points (moderate impairment) after 3 weeks of treatment (FIGURE 2) [55]. In patients who received lithium or divalproex only, mean GAS scores increased from 36.3 (major functional impairment) to 47.79 (serious functional impairment) over the same period.

In the ziprasidone monotherapy study, mean GAS scores improved from 38.1 points (major functional impairment) to 53.4 points (moderate functional impairment), compared with an improvement from 38.2 (major functional impairment) to 46.5 points (serious functional impairment) in those receiving placebo (FIGURE 2) [63].

Similarly, in the risperidone monotherapy study, GAS scores improved from a mean of 35.8 (major functional impairment) to 66.9 points (moderate functional impairment) over the initial 3 weeks of active treatment (FIGURE 2) and to 77.7 points (no more than slight functional impairment) after a further 9 weeks of treatment [62].

Taken together and with the provisos mentioned above, these data suggest that quetiapine, ziprasidone and risperidone offer broadly equivalent improvements in functional status within the first 3 weeks of treatment in patients with bipolar mania. Evidence from longer-term trials indicates that the benefits of treatment with quetiapine and risperidone for HRQoL increase further over time [52,53,62].

The olanzapine studies employed the SF-36, Q-LES-Q and QOLI in the assessment of HRQoL in mania trials. The two studies that employed the SF-36 support the ability of olanzapine to return patients' mean scores towards published community norms, although differences from these normative values appeared to persist even after 6 weeks of treatment, most notably for social functioning and role–emotional subdomains (FIGURE 3).

### HRQoL outcomes in bipolar depression studies

Two large, well-designed, placebo-controlled studies in bipolar depression have been published, one for quetiapine and one for olanzapine (TABLE 3). These studies used the short form of the Q-LES-Q and the SF-36, respectively, to measure HRQoL.

### Quetiapine

In the BipOLar DEpRession (BOLDER) I, a double-blind, placebo-controlled trial, 542 patients with bipolar I or II disorder experiencing a major depressive episode were randomly assigned to receive quetiapine at a fixed dose of either 300 or 600 mg/day or placebo for 8 weeks [64]. Both quetiapine doses significantly improved depressive symptoms compared with placebo, measured by change in the MADRS score, and the benefit for quetiapine emerged as early as the first week of treatment. Recently, these outcomes have been confirmed in the BOLDER II trial [40].

The 16-item short-form of the Q-LES-Q was adopted in BOLDER I to assess HRQoL (TABLE 3) [65]. Quetiapine monotherapy (300 and 600 mg/day) produced significantly greater improvement in HRQoL compared with placebo both at the first assessment of HRQoL (4 weeks), and at end point (8 weeks) (FIGURE 4) [65]. Analysis of effect sizes supports the significant benefit for quetiapine at both doses in these assessments (FIGURE 5).
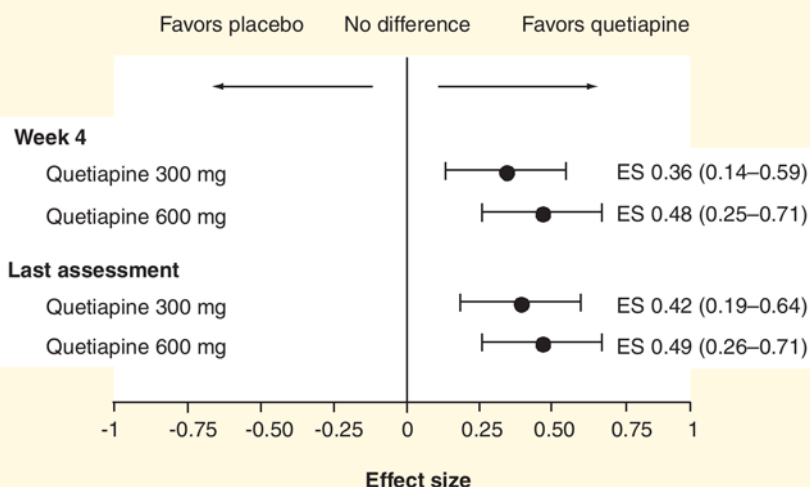
Figure 5. Effect size for Q-LES-Q % score (quetiapine versus placebo) and 95% confidence intervals at week 4 and last assessment during 8 weeks' treatment with quetiapine (300 or 600 mg/day) or placebo among adult patients with bipolar I or II depression. Effect size (ES) is calculated as the absolute difference between treatment groups divided by the pooled standard deviation Q-LES-Q: Quality of Life Enjoyment and Satisfaction Questionnaire. [5].

These authors also observed a significant correlation between the improvement in HRQoL and the improvement in depressive symptoms measured by the primary efficacy measure, MADRS, and a secondary efficacy measure, the Clinical Global Impression of Illness scale [65].

### Olanzapine

In a study of olanzapine in 833 patients with bipolar I depression, olanzapine as monotherapy and olanzapine combined with fluoxetine were significantly superior to placebo at 8 weeks by the primary efficacy measure of MADRS score change; olanzapine–fluoxetine was found to be superior to olanzapine monotherapy [66]. In an analysis of the trial, Shi and colleagues examined changes in HRQoL at 8 weeks based on the SF-36 (TABLE 3) [67]. In terms of overall treatment effect, olanzapine monotherapy did not offer significantly greater improvement in HRQoL than placebo, whereas the olanzapine–fluoxetine combination was superior to both placebo and olanzapine. SF-36 subscale analyses for olanzapine, olanzapine–fluoxetine and placebo indicate consistently greater benefit for olanzapine–fluoxetine than olanzapine alone (FIGURE 6).

### Comparing the effects of quetiapine & olanzapine on HRQoL in bipolar depression

The studies described above on quetiapine and olanzapine employed different instruments to assess change in HRQoL during pharmacotherapy (Q-LES-Q and SF-36, respectively). This, and the differences in the study populations, precludes direct cross-study comparisons, although limited interpretation may be attempted.

In the analysis by Endicott and colleagues, patients treated with quetiapine 300 or 600 mg/day for 8 weeks achieved scores of 55 and 56 points, respectively, significantly greater than the 46-point score in the placebo group [65].

In the olanzapine study, the olanzapine–fluoxetine combination was more effective than olanzapine monotherapy in returning patients toward published normative values. However, clinically relevant (>10-point) differences from normal persisted even after 8 weeks of olanzapine–fluoxetine treatment, for five of the eight subdomains (mental health, role–emotional, role–physical, social functioning and vitality).

Bipolar depression makes the greatest contribution to reduced HRQoL in bipolar disorder, and these results for quetiapine and olanzapine are encouraging for the improvement of HRQoL with pharmacotherapy. Individual patients may return toward levels of functioning comparable with the general population. In the case of quetiapine, significant benefit was demonstrated by 4 weeks of treatment.

### Adverse events & HRQoL

Adverse events from medications used in bipolar disorder impact on HRQoL. These impacts may be direct, as a consequence of the burden of the events themselves, and indirect, by their contribution to nonadherence to therapy and likely relapse of symptoms.

Rates of nonadherence and poor adherence to medications in bipolar disorder are high and they appear to be related, in part, to the experience of adverse events; although other factors (including concerns over dependency) may have a greater impact [68,69]. Potential adverse effects reported for certain atypical antipsychotics such as weight gain and the risk of metabolic changes, extrapyramidal symptoms, somnolence and hyperprolactinemia with sexual dysfunction may have the greatest propensity to impact on treatment adherence and HRQoL. Indeed, a direct correlation has been demonstrated between weight gain and reduced HRQoL in patients treated with olanzapine or divalproex [60]. Quetiapine was not associated with an increased risk of extrapyramidal side effects in the mania trials and its effects on weight are lesser than with older atypical antipsychotics [54,70]. Furthermore, quetiapine did not raise prolactin levels or produce frequent reproductive or sexual side effects in the mania and bipolar depression trials, respectively [54,64].

Measures for assessing functioning and HRQoL capture, in part, the burden of adverse events as well as the alleviation of symptoms associated with successful therapy. The
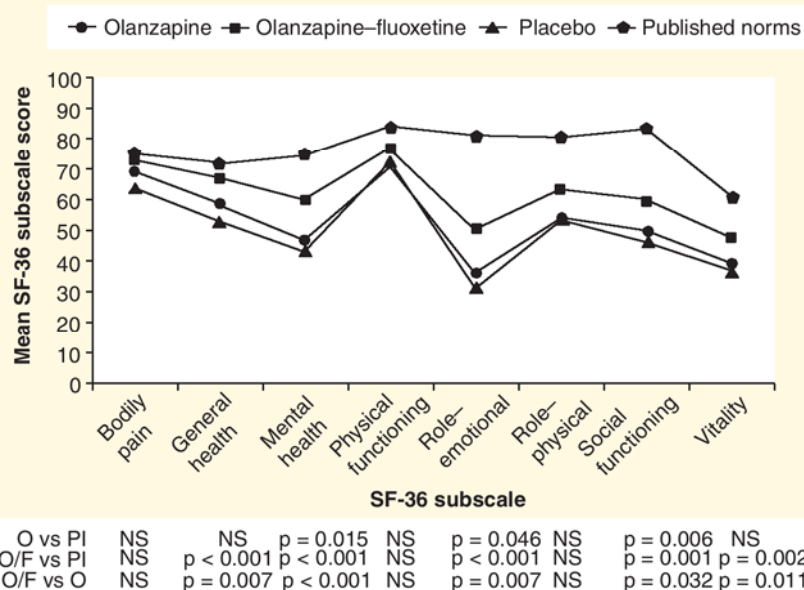
Figure 6. Improvement in health-related quality of life assessed using the SF-36 short form during 8 weeks' treatment with olanzapine (5-20 mg/day), olanzapine–fluoxetine combination (6/25, 12/25 or 12/50 mg/day) or placebo among adult patients with bipolar depression [67] compared with published normative values [30]. NS: Not significant; O: Olanzapine; O/F: Olanzapine–fluoxetine; PI: Placebo; SF-36: 36-Item Short Form Inventory.

improvement than placebo in HRQoL, measured by the short-form Q-LES-Q. These improvements were observed at the first HRQoL assessment at 4 weeks after treatment initiation. For olanzapine monotherapy, overall improvement in HRQoL measured by SF-36 did not differ significantly from placebo and was inferior to the improvement provided by olanzapine–fluoxetine.

Where analyses have been performed in bipolar depression, the efficacy of treatment correlates with improvements in functionality and HRQoL. By contrast, the adverse effects of medications may reduce HRQoL, both directly and indirectly via treatment adherence. Medication choice should be tailored to the individual patient, taking into account the patient's risk profile and how the efficacy and tolerability profiles of potential medications might impact on HRQoL. The favorable efficacy and tolerability profile of quetiapine in mania and bipolar depression may be relevant characteristics from this viewpoint.

improvements in these measures with quetiapine and other medications reflect the net benefit to quality of life and functioning that these agents offer.

### Expert commentary

Bipolar disorder has a major impact on functioning and HRQoL during all phases of the illness. Emerging data suggest that pharmacotherapy improves functioning and HRQoL, although further trials are required to quantify these benefits with formal and standardized measures. Very recent data suggest that adjunctive psychotherapy may offer additional benefit in these domains [37]. Consensus on the choice of instrument would facilitate comparison between medications. In the absence of a disease-specific instrument, a combination of physician assessment using, for example, the GAS or GAF as a measure of functioning, and a self-report assessment using the Q-LES-Q or SF-36 for HRQoL, may provide valuable information.

In studies of atypical antipsychotics for bipolar mania, clinically relevant improvements in functioning emerged within 3 weeks of initiating treatment with quetiapine, comparable with ziprasidone and risperidone. Different instruments were used in the olanzapine trials, where although HRQoL improved during the first few weeks of treatment, assessment of SF-36 subdomains suggested that clinically relevant deficits persisted even after 6 weeks of treatment and that there may be a lag between symptomatic and functional improvement.

For patients with bipolar depression, quetiapine monotherapy (300 or 600 mg/day) offered significantly greater

### Five-year view

This review identifies several unmet needs, a proportion of which may be successfully fulfilled in the next 5 years.

The foremost need is for a validated, disease-specific instrument to assess HRQoL in bipolar disorder that can be adopted as a standard in future trials. This would assist comparisons of different medications in bipolar disorder. Investigations in this area are under way (such as by McLeod and colleagues [27]).

Accompanying this, it may be possible to explore more fully the effects of medications across the range of HRQoL sub-domains and the effects of mood state changes on these sub-domains. The benefits of treatments on comorbidities and the influence of these changes on HRQoL may also be investigated.

Maintenance studies are awaited to characterize the timescale of improvements in HRQoL and functioning, and to confirm long-term benefits in this chronic disorder.

The role of adjunctive psychotherapy in enhancing the benefits of pharmacotherapy for long-term outcome may receive greater attention.

These developments, if achieved, will provide insights into the profile of improvements possible in functioning and HRQoL with the treatments available.

## Key issues

- Bipolar disorder has a major impact on functionality and health-related quality of life (HRQoL) during all phases of the illness.

- Pharmacotherapy for bipolar disorder during manic and depressive episodes improves HRQoL from both the patient's perspective using self-assessment tools and from the physician's viewpoint using physician-based assessments of functioning, and symptom-based measures of treatment efficacy.

- The efficacy of a medication to improve manic and depressive symptoms appears to correlate with improvements in functioning and HRQoL, although the latter may lag in time to a variable degree.

- Quetiapine, either as monotherapy or added to lithium or divalproex, offers clinically relevant improvements in functioning in mania, which are apparent within 3 weeks of initiating treatment, comparable with those for ziprasidone and risperidone. The benefits of quetiapine were sustained to the 12-week end point. Some delayed QoL benefits with olanzapine have been demonstrated.

- For patients with bipolar depression, quetiapine monotherapy offers significant improvement in HRQoL by 4 weeks, the first assessment after initiating treatment. As in the mania monotherapy trials, improvements in functioning in bipolar depression were maintained to study end at 8 weeks. In contrast, only the combination of olanzapine and fluoxetine, but not olanzapine monotherapy, has been associated with QoL benefit at 8 weeks.

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