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Review article

Allopurinol as add-on treatment for mania symptoms in bipolar disorder: systematic review and meta-analysis of randomised controlled trials

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Background
Since bipolar disorder seems to be associated with purinergic system dysfunction, allopurinol might be effective in treating symptoms of mania.

Aims
To estimate the efficacy and tolerability of allopurinol as adjunctive treatment for mania symptoms in people with bipolar affective disorder.

Method
We conducted a systematic review and meta-analysis of randomised controlled trials (RCTs) comparing the effects of adjunctive allopurinol and placebo on mania symptom changes.

Results
Five RCTs were included in the meta-analysis. Participants with allopurinol augmentation had a significantly greater decrease in mania symptoms than those with placebo (SMD = −0.34, $P = 0.007$), especially in people with the most severe forms of mania. Remission rates, although based on only two studies ($n = 177$), were significantly higher among individuals receiving allopurinol, whereas for discontinuation and side-effects no difference was found.

Conclusions
Our finding of a small to moderate effect size and overall low evidence for add-on allopurinol in reducing mania symptoms indicate that its use in routine practice needs further elucidation.

Declaration of interest
None.

Allopurinol is a xanthine oxidase inhibitor, approved by the Food and Drug Administration (FDA) for the clinical management of gout and hyperuricaemia, decreasing uric acid levels by preventing purine degradation.[1] Its use has been proposed in treatment-resistant mania associated with hyperuricaemia,[2] since uric acid – the end-product of purine metabolism – seems involved in the regulation of mood, sleep, appetite, social interaction and impulsivity.[3] It has been proposed that bipolar affective disorder might be associated with a purinergic system dysfunction,[4] showing, particularly in the manic phases of the illness, higher levels of plasma uric acid than those in both healthy people,[5] and in people affected by other mental disorders.[6] In addition, uric acid levels in manic phases seem significantly higher than in euthymic or depressive ones,[7,8] and hyperthymic and depressive temperaments have been related respectively to high and low levels of uric acid.[9] Finally, lithium, one of the most effective medications for treating bipolar disorders,[10] was originally studied as a therapeutic option by lowering the uric acid concentration in plasma.[11] In sum, there might be a plausible biological and clinical rationale for allopurinol use in treating symptoms of mania in people with bipolar disorder. A previous meta-analysis,[12] testing purinergic modulators for the treatment of both schizophrenia and bipolar disorder, investigated the effect of allopurinol on manic symptoms. However, methodological issues such as the lack of risk of bias and quality assessments, the heterogeneity of outcome measures chosen, the absence of appropriate subgroups and sensitivity analyses, as well as the limited sample size from available studies, made it impossible to draw firm conclusions. In addition, two recently published trials have shown mixed results.[13,14] Thus, a body of evidence of acceptable size has accumulated, possibly overcoming the limitations of previous research in exploring the efficacy and tolerability of allopurinol for treating people with bipolar disorder. Studying new treatments for bipolar disorder is important because a significant proportion of patients still fail to respond to standard therapeutic options with mood stabilisers and second-generation antipsychotics.[3,15,16] We report a systematic review and meta-analysis of randomised controlled trials (RCTs) that compared efficacy and safety of adjunctive allopurinol against placebo, aiming to clarify its role in treating symptoms of mania in people with bipolar disorder.

Method

This systematic review and meta-analysis was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[17] The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42015025120).

Eligibility criteria

We included RCTs that compared adjunctive allopurinol with placebo for the treatment of symptoms of mania, along with standard mood stabilisers and/or antipsychotic treatment. To be considered, studies had to recruit adults with bipolar disorder experiencing a manic or mixed episode, from any in-patient or out-patient setting.

Outcomes

The primary outcome was efficacy, as measured by mean overall change (from baseline to end-point) in mania symptoms assessed with any appropriate rating scale, including (but not limited to) the Young Mania Rating Scale (YMRS).[18] Secondary outcomes were remission, all-cause discontinuation and side-effects. Remission was defined as a score less than or equal to the standard cut-off of the chosen measure (12 on the YMRS total score).[18] All-cause discontinuation (acceptability) was estimated by

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calculating the number of participants who left the study early for any reason before reaching their end-point. Finally, we assessed differences in frequencies of side-effects occurring in 5% or more of individuals from at least two different studies.

Search strategy

Computerised PubMed, Cochrane Library and PsycINFO (via ProQuest) searches were performed from database inception until August 2015. We searched ClinicalTrials.gov (search date 19 August 2015) for all unpublished intervention studies. There was no language restriction. Index and free-text search terms included 'allopurinol' AND ('bipolar' OR 'mania' OR 'manic'). Two authors (F.B. and G.C.) independently performed the preliminary screening based on titles and abstracts, to include potentially relevant articles. After the first screening, studies were retrieved in full text to check eligibility according to inclusion and exclusion criteria.

Data extraction

We developed a sheet for the extraction of the main information from each included study: year of publication, study location, setting, inclusion criteria, sample size, participants' characteristics, tested allopurinol dose and standard treatment, follow-up duration and main results. Two authors (F.B. and G.C.) independently conducted data extraction, and discordances were resolved by consensus with the co-authors (C.C. and M.C.). When reported information was unclear or ambiguous, the relevant corresponding author was contacted (by F.B.) for clarification.

Risk of bias and quality of evidence

We followed the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) for grading the quality of evidence as high, moderate, low or very low, according to the standard items.[19] We used the standard Cochrane Collaboration tool for assessing risk of selection, performance, detection, attrition, reporting and other biases.[20] Selection bias was assessed by evaluating the appropriateness of random sequence generation and allocation concealment. Performance and detection bias were evaluated by checking whether masking of participants/personnel and outcome assessors respectively was guaranteed. Attrition bias was ascertained assessing proportions and balance of withdrawals from the trial between groups leading to incomplete outcome data, and strategies implemented to deal with this issue. We considered at low risk of bias studies with attrition rates of 20% or below in either study arm,[21] or those using full ('as randomised') or modified (excluding only randomised participants dropping out before receiving treatment) intention-to-treat (ITT) analyses for primary outcome.[22] Reporting bias was evaluated by checking first that data on key outcomes – efficacy, discontinuation rates and side-effects – were provided, and second that a previously registered study protocol with sufficient agreement with the final manuscript was available. Finally, to classify studies for 'other biases', we considered authors' potential conflicts of interest and potential sources of indirectness,[19] taking into account whether standard treatment for bipolar disorder was comparable between allopurinol and control groups or whether further treatment differences, potentially influencing clinical response, could be identified. Two authors (F.B. and G.C.) independently assessed the risk of bias. Differences in the evaluation were resolved by consensus with the other authors (C.C. and M.C.). Graphical summaries of risk of bias were created using RevMan version 5.2.

Statistical analysis

For the primary outcome (efficacy) we used either mean overall change (from baseline to end-point in both allopurinol and placebo groups) on mania symptom scores (with standard deviations or standard errors) or relevant *t*-test values, to estimate standardised mean differences (SMDs) with 95% confidence intervals. Individual SMDs were pooled in a meta-analysis by the inverse variance method using random effects models. Intention-to-treat data, with last observation carried forward (LOCF) analyses, were used. A subgroup analysis was carried out to explore whether studies selecting people with manic episodes and those including also people with mixed episodes showed different effect sizes. We used the I^2 test for subgroup differences to assess the variability in effect estimates that was due to genuine differences rather than chance.[23] In addition, we used meta-regression to test potential differences across studies due to other characteristics, including follow-up duration (4 weeks *v.* longer), allopurinol dosage (300 mg/day *v.* different dosages) and standard treatment for bipolar disorder (lithium *v.* other treatments), using the Monte Carlo permutation test for meta-regression with moment-based estimate of between-study variance. Finally, a sensitivity analysis was performed omitting the studies with high or unclear risk of bias on selected items (selection, performance, detection, attrition, reporting and other bias).

For secondary outcomes (remission, discontinuation and side-effects) rates between allopurinol and placebo groups were compared using random effects risk ratio (RR). Statistical significance was set at $P<0.05$ and results were summarised using conventional forest plots. Heterogeneity was estimated using both P values from Cochran's Q-test and the I^2 index, with values of 25%, 50% and 75% taken to indicate low, moderate and high levels of heterogeneity respectively.[24] Finally, testing for publication bias, we used Egger's test if at least ten studies were included in the meta-analysis, as recommended.[25] Analyses were performed using Stata statistical software package version 13.1.

Results

Our search generated 13, 10 and 10 records from PubMed, Cochrane Library and PsycINFO (via ProQuest) respectively. After removing duplicates and including one additional record from ClinicalTrials.gov, there were 19 studies to be screened (Fig. 1). The preliminary screening by reading titles and/or abstracts identified 13 potentially eligible studies. After screening full texts we excluded eight studies: three conference abstracts, three letters or commentaries, one review and a trial protocol on allopurinol augmentation for prevention of mania that was not relevant. Five RCTs met our inclusion criteria and were included in the meta-analysis.[13,14,26–28] All manuscripts were written in English. The studies, published between 2006 and 2014, were based on in-patient and/or out-patient samples, and were from Iran, Brazil, Romania and the USA. All studies used the YMRS to measure symptoms. Duration of follow-up ranged between 4 weeks and 8 weeks. Detailed characteristics of included studies are summarised in online Table DS1. We obtained unpublished data from two studies,[13,28] contacting relevant corresponding authors who provided information on YMRS mean changes (with standard deviations) in both allopurinol and placebo groups,[13,28] as well as remission rates based on the YMRS standard cut-off score of 12.[13]

Risk of bias

Graphical assessments of the risk of bias are reported in online Figs DS1 and DS2.

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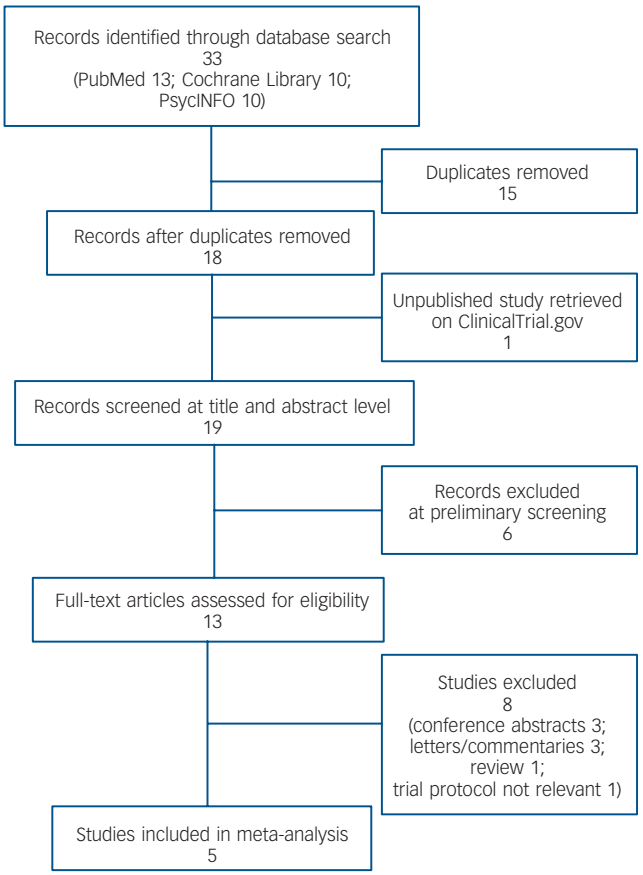

Fig. 1 Study selection.

Selection bias

Two studies clearly described appropriate methods for random sequence generation, with a computer-based number generator,[13,26] whereas in the other studies methods were unclear.[14,27,28] Appropriate methods for allocation concealment were described in all studies but one, which provided no information on allocation method.[27]

Performance and detection bias

All studies were double-blind RCTs and blinding (masking) of participants and personnel, as well as of outcome assessors, was satisfactorily guaranteed with low risk of performance or detection bias.

Attrition bias

All studies adopted approaches to dealing with attrition bias, using ITT data and including LOCF of people who left the study. Two studies used a full ITT approach, taking into account for primary analyses all randomised participants.[14,26] Two other studies used modified ITT, excluding from primary outcome analyses randomised individuals withdrawing before participating in any of the study stages.[13,27] However, one study might have been influenced by some degree of attrition bias since it did not use a proper ITT approach, excluding from primary outcome analyses a high proportion of randomised participants (25% and 23% of those on allopurinol and placebo respectively) who discontinued the intervention early.[28]

Reporting bias

Three studies provided complete data on key outcomes,[14,26,28] whereas two studies did not report clear and detailed findings on frequency of different side-effects occurring among the allopurinol and placebo groups respectively.[13,27] However, among studies with complete data, one study did not have a protocol,[26] whereas another had a protocol registered after the study completion.[28] Only one study had a protocol with sufficient agreement with the final manuscript;[14] all the other studies were therefore judged as being at high or unclear risk of reporting bias.

Other bias

One study reported some potential conflict of interest,[27] whereas the others did not disclose any financial influence.[13,14,26,28] Furthermore, three studies used identical (or convincingly comparable) standard treatments for bipolar disorder in both allopurinol and placebo arms, i.e. 1–1.2 mEq/L lithium plus 10 mg haloperidol,[26] flexible doses of lithium according to relevant plasma levels,[28] and 15–20 mg/kg of sodium valproate.[13] On the other hand, potential indirectness bias in terms of comparability of standard treatments for bipolar disorder between allopurinol and control groups was found in two studies that included people treated with a wide range of psychopharmacological agents for bipolar disorder (unspecified and mixed mood stabilisers and/or atypical antipsychotics).[14,27]

Synthesis of results

The included studies screened for eligibility 679 participants, of whom 469 met inclusion criteria and were randomised to receive allopurinol ($n=236$) or placebo ($n=233$). An overall sample of 433 participants, 218 receiving allopurinol and 215 placebo, were analysed for the primary outcome. Among these, 364 participants, i.e. 78% of those randomised, completed the trials (184 from the allopurinol arms and 180 from the placebo arms).

Efficacy

Decrease of mania symptoms (from baseline to end-point) as measured by the YMRS was significantly more marked among people taking allopurinol compared with those taking placebo (SMD = −0.34, 95% CI −0.60 to −0.09; $P=0.007$). Heterogeneity was low to moderate ($I^2=35\%$, $P=0.18$), and subgroup analysis of studies restricted to people with manic episodes showed an effect of add-on allopurinol ($P<0.001$) that was not seen in studies including participants with mixed episodes ($P=0.64$) (Fig. 2). The test for subgroup differences was significant ($P=0.02$). According to the meta-regression analysis, allopurinol dosage ($P=0.50$), follow-up duration ($P=0.41$) and standard treatment chosen ($P=0.59$) did not influence the results of the meta-analysis. Sensitivity analyses, omitting studies with high or unclear risk of bias on selected items, are reported in Table 1. Publication bias was not formally assessed, as fewer than ten studies were included in our review.

Remission

Data on remission were available from two studies,[13,28] accounting for 177 participants. The pooled RR of clinical remission was 1.51 (95% CI 1.20 to 1.90, $P<0.001$; $I^2=0\%$) in people taking allopurinol compared with those taking placebo.

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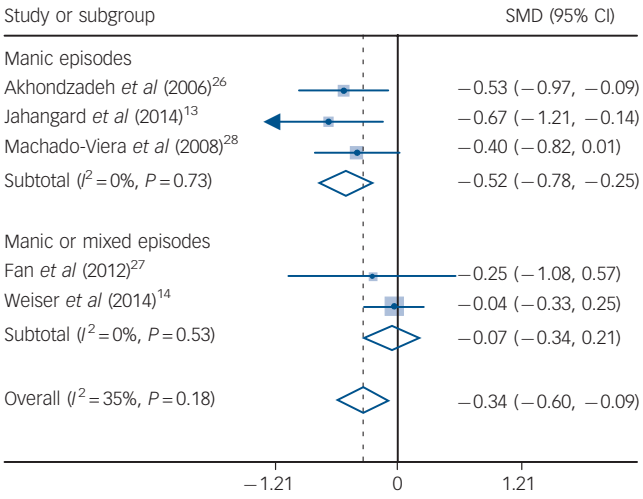

Fig. 2 Change from baseline to end-point in symptoms of mania: standardised mean differences (SMD) for adjunctive allopurinol *v.* placebo.

Discontinuation

Data on discontinuation were available for 469 participants (236 receiving allopurinol and 233 placebo). The meta-analysis showed no difference in all-cause discontinuation between allopurinol and placebo, with a RR of 0.91 (95% CI 0.66 to 1.26, $P = 0.58$) and no heterogeneity across studies ($I^2 = 0\%$, $P = 0.43$).

Side-effects

Data on rates of side-effects were available in three of five included studies,[14,26,28] since others used continuous scores,[27] or provided unclear information on differences in side-effect frequencies between index and control groups.[13] Details of specific side-effects showed no difference in those more frequently observed, i.e. asthenia ($P = 0.78$), diarrhoea ($P = 0.75$), dizziness ($P = 0.73$), headache ($P = 0.41$) and somnolence ($P = 0.59$). No serious adverse event was reported. All detailed findings, with relevant effect sizes, included studies, sample sizes and heterogeneity, are summarised in online Table DS2.

Discussion

To our knowledge, this is the first meta-analysis systematically evaluating data on efficacy and relevant secondary outcomes, as well as quality of evidence, of adjunctive allopurinol for treatment of symptoms of mania. Compared with previous meta-analyses, our review included two new, large RCTs, doubling the overall sample size.[13,14] According to findings from five RCTs, adjunctive allopurinol in people with bipolar disorder showed higher efficacy in decreasing mania symptoms compared with placebo. The low to moderate statistical heterogeneity across studies added consistency to our findings. According to estimated SMD, we found a small to medium effect of add-on allopurinol.[29] The results were confirmed by relevant meta-regression analysis, highlighting that findings were not influenced or moderated by differences between studies in terms of allopurinol dosage, follow-up duration or standard treatment for bipolar disorder. Furthermore, we found that studies selecting people with a current manic episode showed a higher pooled effect size.[13,26,28] Relevant SMDs supported a medium effect for adjunctive allopurinol among individuals with manic episodes.[29] On the other hand, according to the relevant subgroup analysis, allopurinol did not show a significant effect in studies selecting also individuals with bipolar mixed features. Therefore, we can reasonably assume that adjunctive allopurinol could be an effective therapeutic option for people experiencing the most severe forms of bipolar disorder in terms of mania symptoms at baseline. Results for secondary outcomes – remission, discontinuation and tolerability – supported a potentially effective role for add-on allopurinol. Although data were available from only two studies,[13,28] we found a small but significant effect in terms of remission rates, with people taking allopurinol 1.5 times more likely to have remission of their symptoms compared with those taking placebo. Furthermore, allopurinol was not associated with treatment discontinuation, showing drop-out and all-cause discontinuation rates comparable with placebo. Finally, allopurinol seems a safe therapeutic option, as no significant risk of side-effects was found, even taking into account those more commonly reported, such as asthenia, diarrhoea, dizziness, headache and somnolence.

Quality of evidence and limitations

Despite early promising findings, evidence supporting adjunctive allopurinol for symptoms of mania should be considered at best 'low', following GRADE standard items. We uncovered at least two factors downgrading quality of evidence: first, although relevant sensitivity analyses confirmed the effect of allopurinol in decreasing mania symptoms, we found some important limitations, notably a potential risk of selective reporting among included studies. Second, reported effect sizes of outcomes, although consistent, were generally imprecise, with large confidence intervals, owing to the small sample size. A more conservative approach, considering both indirectness (due to non-comparable treatments found in two studies) and the uncertain probability of publication bias, would suggest further downgrading evidence to a 'very low' level. However, indirectness seemed to decrease rather than increase the effect size of allopurinol. Indeed, the relevant sensitivity analysis, excluding studies with heterogeneous treatments, showed a greater efficacy for allopurinol. Thus, we could be confident that the effect size of allopurinol was not inflated by an indirectness-related bias. Furthermore, it was impossible to assess statistical significance

Table 1 Sensitivity analyses categorised by risk of bias

	Available studies[a]	Allopurinol group *n*	Placebo group *n*	SMD (95% CI)	*P*	I^2, %
Low risk of selection bias due to random sequence generation	2	71	68	−0.59 (−0.93 to −0.25)	<0.001	0
Low risk of selection bias due to allocation concealment	4	206	204	−0.36 (−0.66 to −0.07)	0.015	51
Low risk of attrition bias	4	173	169	−0.35 (−0.68 to −0.01)	0.043	49
Low risk of bias due to conflicts of interest	4	206	204	−0.36 (−0.66 to −0.07)	0.015	51
Low risk of bias due to heterogeneous treatment	3	116	114	−0.52 (−0.78 to −0.25)	<0.001	0

SMD, standardised mean difference.
a. Only one study had a low risk of reporting bias and all studies had low risks of performance and detection bias, thus no sensitivity analyses were carried out.

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of publication bias, and we did not contact pharmaceutical companies or governing bodies involved in pharmaceutical market authorisation procedures to enquire whether any other RCTs had been undertaken with allopurinol given to participants with bipolar disorder. However, it seems unlikely that further RCTs in this field remained unpublished, since we searched three different electronic databases and comprehensively explored a trials register (ClinicalTrials.gov). Finally, even if we assume that studies not using full ITT analyses might have inflated positive reporting, this involved just one study. In sum, our findings should be interpreted with caution given both the small number of included RCTs meeting our inclusion criteria and the resulting limited overall sample size, as well as other reported quality issues.

Implications for practice and research

Adjunctive allopurinol shows a small to medium effect size on symptoms of mania in people with bipolar disorder. However, its effect, although statistically significant, seems small to be considered clinically meaningful. Taking into account standards developed to produce recommendations, evidence from this meta-analysis should be considered low in quality.[19] Nevertheless, owing to the significant effect of indirectness on results of this meta-analysis, further research with rigorously defined treatment patterns for both intervention and control groups is needed in order to confirm confidence in our findings. Allopurinol could be considered as a promising therapeutic option, in addition to standard treatment with mood stabilisers and/or second-generation antipsychotics, especially for the most severe forms of bipolar mania. Its efficacy seems clearer in studies including participants with manic episodes and excluding those with mixed episodes. Of course, before its benefits can be claimed, the relevant level of evidence should be improved and its efficacy and tolerability further explored in large multicentre RCTs, possibly based only on people with manic episodes. Moreover, since all available RCTs had short follow-up periods (4–8 weeks), long-term data are also needed in order to explore the safety of this drug and its potential role in maintenance treatment. Unfortunately, there is a lack of studies in this area, with only one research protocol with unknown results registered so far (ClinicalTrials.gov NCT00732251). Furthermore, caution is needed also in interpreting results on tolerability of allopurinol, since this was assessed only during the acute treatment phase (with a maximum follow-up of 8 weeks), whereas the long-term safety in people with bipolar disorder remains unknown. In addition, allopurinol adverse effects could be more severe in people with bipolar disorder,[30] possibly because of concomitant medication with mood stabilisers and atypical antipsychotics inducing additional side-effects.[31] On the other hand, it is not possible to suggest an optimal allopurinol dosage, since included RCTs used heterogeneous dosages and relevant meta-regression did not show a dose–response relationship.

Finally, although a biological rationale for allopurinol use in clinical practice can be found in increased uric acid levels in people with bipolar disorder during manic and mixed episodes, further research is required to clarify the role of purinergic dysfunction in the pathophysiology of bipolar disorder.[3,8,32]

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EXTRA CONTENT ONLINE

psychiatry in literature

Sylvia Plath's bell jar of depression: descent and recovery

Hannah Marcarian, Paul O. Wilkinson

The Bell Jar is a 1963 novel by Sylvia Plath describing the decline of main character Esther into a depressive episode and her stay in a psychiatric ward. Plath herself had recurrent depression and was hospitalised for this. She completed suicide a month after the book's publication. Her own understanding-by-experience may have helped her to write about depression both accurately and powerfully.

There are hints of Esther's depressive symptoms starting while she interns at a New York magazine during her summer vacation. She is unmotivated to take part in events and does not feel enjoyment. Esther describes her low mood as feelings of sadness and tiredness and realises that she has not felt truly happy since the age of 9, before her father died. She portrays how lonely she feels in a busy place and frequently thinks of death. Esther has succeeded throughout her life academically, gaining a scholarship to college, but feels inadequate and struggles to choose a path for the future.

The night before Esther leaves New York, she is sexually assaulted at a party. On her return home, she finds out that she has been rejected from a summer writing course. With this plan no longer in place, Esther feels hopeless and her depression worsens. She does not make further arrangements for any summer school, instead planning to write a novel. However, she is unable to concentrate and soon gives up on the idea of writing. She lacks enjoyment in activities she previously enjoyed and lacks structure in her days, entering a cycle of sadness – no motivation – no enjoyable activities – sadness. Her self-esteem suffers. She stops taking care of her personal appearance, wearing the same clothes for weeks and not washing, as she cannot see the point. She has difficulty sleeping and is referred to a psychiatrist who she doesn't believe will be able to help, a further sign of her hopelessness.

Esther frequently contemplates suicide and describes her attempts in a methodical, matter-of-fact manner, almost as if she does not think they would bother the reader. This seems to reflect the lack of connectedness she has with her mother and other people, which has now been demonstrated as a potent risk factor for suicide attempts (Klonsky & May's 'ideation-to action' theory).

Esther takes a large overdose and is admitted to a psychiatric hospital. She takes time to trust doctors, but eventually improves following appropriate care and treatment. The 'bell jar' of the title is a beautiful metaphor, describing the heavy lid over Esther, filled with her own sour air, that eventually lifts slightly, allowing some fresh air into her life.

As well as describing depression vividly, we are told about multiple risk factors, making this case so realistic. Esther deteriorates from low-level sadness and anhedonia to a severe depressive episode following two adverse life events. However, she also has several predisposing factors: her father died when she was young and she has not grieved this, probably due to the attitudes of her mother. She is not close to her mother, and hardly sees her when in hospital, suggesting a poor attachment. She does not mention good long-term friends either before or during her time at college. She has high expectations of others, but disregards them when these are not met.

The Bell Jar is a very powerful and believable description of depression, which will be recognised by those who have been affected and enlighten those who have not. It also offers some hope that no matter how severe the depression is, people can recover.

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