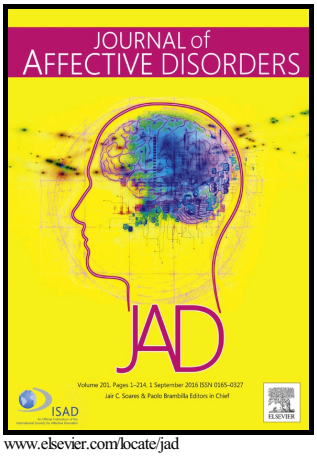
DOI:
10.1016/j.jad.2017.04.019

Document Version
Peer reviewed version

Citation for published version (APA):
Young, A. H., Evitt, L., Brignone, M., Diamand, F., Atsou, K., Campbell, R., Cure, S., & Danchenko, N. (2017). Cost-utility evaluation of vortioxetine in patients with Major Depressive Disorder experiencing inadequate response to alternative antidepressants in the United Kingdom. *Journal of Affective Disorders*, *218*, 291-298. https://doi.org/10.1016/j.jad.2017.04.019



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PII: S0165-0327(16)32206-6
DOI: http://dx.doi.org/10.1016/j.jad.2017.04.019
Reference: JAD8893

To appear in: *Journal of Affective Disorders*

Received date: 28 November 2016
Revised date: 10 March 2017
Accepted date: 16 April 2017

Cite this article as: A.H. Young, L. Evitt, M. Brignone, F. Diamand, K. Atsou, R. Campbell, S. Cure and N. Danchenko, Cost-utility evaluation of vortioxetin in patients with Major Depressive Disorder experiencing inadequate response t alternative antidepressants in the United Kingdom, *Journal of Affectiv Disorders,* http://dx.doi.org/10.1016/j.jad.2017.04.019

Cost-utility evaluation of vortioxetine in patients with Major Depressive Disorder experiencing inadequate response to alternative antidepressants in the United Kingdom

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Abstract

Background

Patients frequently require several lines of therapy for treatment of major depressive episodes. This economic analysis details the management of patients who responded inadequately due to lack of efficacy or intolerability to two previous antidepressants in the UK.

Methods

The model included a decision tree and a Markov component. Health states considered in the decision tree were remission, response, no response, withdrawal due to adverse events, relapse, recovery, and recurrence. The time horizon was 24 months. Patients were on third-line treatment for up to a 3-month acute phase and a 6-month maintenance phase. As third-line efficacy data were not available, inputs were calculated by adjusting original second-line data to third-line based on proportionate reductions observed in STAR*D. Equivalent efficacy was assumed for all comparators. Healthcare resource use and utilities were based on UK estimates.

Results

Vortioxetine was a cost-effective treatment option at a threshold of £20,000/QALY vs. escitalopram, citalopram, sertraline, and was associated with more health benefits, less costs (was dominant) versus relevant third-line comparators venlafaxine and duloxetine. Agomelatine was found not to be a

cost-effective option. The 22-month maintenance phase treatment scenario results were similar to the 6-month base case.

Limitations

Third-line efficacy data were not available. This highlights the need for studies in patients receiving third-line treatment.

Conclusion

This model provides an overview for the management of patients receiving third-line treatment where limited evidence currently exists. Vortioxetine, with its novel mechanism of action, is expected to be a dominant treatment option versus relevant comparators in the UK.

Keywords

Major depressive disorder, depression, cost-utility analysis, inadequate response, vortioxetine.

Introduction/Background

Major Depressive Disorder (MDD) is a common and frequently recurrent mood disorder. MDD as a recurrent disorder comprises at two or more major depressive episodes (MDEs).

This psychiatric disorder is characterized by symptoms interfering with the daily life of patients, such as lack of enjoyment in activities, feelings of sadness, guilt, anxiety, and recurrent thoughts of death and suicide (1). It may also harm the wellbeing of family members, including children. Being the child of a depressed parent carries a greatly increased risk of suffering from depression for the child involved. As many as 40 percent of the children of depressed parents will suffer from depression before 20 years of age (1, 2). The number of adult patients experiencing a moderate-to-severe MDE and receiving switch antidepressant therapy is estimated at approximately 700,000 to 1.2 million per annum based on mid-2013 figures from the Office for National Statistics (ONS) in the United Kingdom (UK) (3) (4). Patients who have encountered multiple episodes or multiple lines of treatment are at a greater risk of suicide attempts (5), hospital admissions (6), and impaired work productivity (7). Therefore, the need to achieve early control in MDD highlights the importance of having effective and well-tolerated treatment options available in the event of inadequate response to a first treatment. In case of absent or minimal response after 8 weeks of treatment, the National Institute for Health and Care Excellence (NICE) CG90 guidelines recommend switching to another antidepressant, newer-generation or different class (8, 9). The NICE guidelines as published by NICE, which is the main health technology assessment body in the UK, provide evidence-based guidance, advice and information services for health, public health and social care professionals. The NICE CG90 guidelines cover identification and management of depression in adults, in both the primary and secondary care settings in the UK.

MDD is associated with heterogeneity in terms of both patients and treatments. Therefore, a strict treatment strategy is unlikely to be optimal, particularly at latter lines of therapy. Due to the recurrent nature of depression, in addition to the high treatment failure rate attributable to inadequate efficacy or intolerability, clinicians aim to match the treatment to the individual, taking into account their treatment and family history, where applicable. This is an approach that is supported by both NICE CG90

guidelines (9) on the treatment and management of depression, and expert opinion. Despite the range of currently available therapies, there is an unmet need for tailored treatments, according to individual patient's profile and history. Such treatments should have a different mode of action and offer equivalent efficacy to other, widely used antidepressants alongside a favourable tolerability profile.

Vortioxetine is an efficacious and well-tolerated, once-daily, orally-administered treatment option for MDD (10). It is an antidepressant with a novel mechanism of action that is thought to work through a combination of serotonin reuptake inhibition and modulation of serotonin receptor activity (10). In addition, pre-clinical and clinical data provide evidence to demonstrate the effect of vortioxetine on cognitive symptoms of MDD (11, 12). Vortioxetine offers significant and clinically relevant improvement in efficacy versus agomelatine (REVIVE; Montgomery et al. 2014) and was generally well tolerated in terms of sexual dysfunction versus escitalopram (TAK 318; Jacobsen et al. 2015).(13) An indirect-treatment-comparison (ITC) was also conducted in switch patients showing that vortioxetine leads to numerically higher remission rates compared with sertraline, venlafaxine, bupropion and citalopram. Vortioxetine is a well-tolerated treatment, with a statistically lower withdrawal rates due to AEs compared with these antidepressants. (14) (15)

Vortioxetine has been recently approved by NICE as an option for treating MDE in adults whose condition has responded inadequately to two antidepressants within the current episode. Detail on the process can be found in the NICE technology appraisal guidance for vortioxetine (TA367) and the Evidence Review Group critique in Lomas 2016. (14, 16)

This paper details the economic model and analysis that was considered in the NICE evaluation of vortioxetine for patients receiving third-line treatment in the UK.

Methods

The population consists of patients who have responded inadequately to two antidepressants within the current episode; referring to third-line in the treatment pathway for their MDE. This includes patients who have experienced a lack of efficacy or/and intolerability to their previous two treatments. The model required making a number of assumptions, which are explicitly described in this section and in the 'limitations' section at the end of this manuscript.

Model structure

In order to ensure the model structure was reflective of UK clinical practice, a comprehensive review of both national and local guidelines, along with current clinical practice through both questionnaires and an advisory board have been undertaken. The structure has been adapted from a model presented in Trivedi et al. 2004 (17), a review on existing models in the NICE depression guidelines (9) and a model developed by The Dental and Pharmaceutical Benefits Agency (TLV) in Sweden (1). Patients were diagnosed using the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria. The DSM diagnostic criteria for MDD are well recognised and widely used in trial settings, with DSM IV being employed in the trials of vortioxetine (18).

The model (available on request) consisted of both a decision tree and a Markov component (Figure 1), with patients entering the model at the third-line of treatment. In the acute phase, patients could follow one of the following 4 clinical pathways: remission, response but no remission, no response, or withdrawal due to AEs. Response was defined as a 50% or more reduction in symptoms from baseline values on Montgomery–Asberg Depression Rating Scale (MADRS) or Hamilton Depression Rating Scale (HAM-D), and remission as MADRS≤10 or HAM-D≤7. Patients who experienced response but no remission at 8 weeks were assumed to be reassessed at week 12. This was informed by clinical opinion which suggested that an additional 4 weeks on treatment would allow for the treatment effect to be fully achieved. If a patient had achieved remission (8 or 12 weeks) or was in response at week 12 they entered the maintenance phase of the model. Patients in no response (8 or 12 weeks) switched to another line of therapy and entered the Markov component. This is consistent with the British Association for Psychopharmacology (BAP) 2015 guidelines which recommend that if a patient has had complete lack of response at 4 weeks and previously failed multiple treatments, they should continue on treatment for another 2-6 weeks. Moreover, clinical experts have suggested that switch at 8 weeks due to no response was reflective of practice (19). Furthermore, a previous cost-utility analyses based on the STAR*D trial shows that switching antidepressants after insufficient response increased remission rates (20). A change of treatment at 4 weeks was assumed for patients

withdrawing due to adverse events, based on internally sourced data, where the majority of patients who stopped treatment due to adverse events withdrew by 4 weeks (21). During the acute phase patients incurred the risk of treatment specific short-term AEs (sexual AEs, dry mouth, nausea, sweating, headache, somnolence, diarrhoea, insomnia and dizziness) which were independent of each other.

The maintenance phase of treatment was considered to be 6 months. This was in line with the minimum recommended treatment period for an antidepressant once symptoms have been resolved and is informed by antidepressant regulatory licenses and NICE guidelines. Once a patient entered the maintenance phase they were subject to a risk of relapse and treatment specific long-term AEs (sexual dysfunction, weight gain and insomnia) which led to treatment switch. A patient who maintained remission for 6 months entered recovery. In this health state the risk of recurrence was considered. Patients who switched to fourth and subsequent lines of treatment or achieved recovery entered the recursive Markov part of the model.

The overall time horizon was 24 months. This allowed for representation of patients with a history of recurrent episodes.

Comparators

In the UK, the initial recommended treatment is a generic selective serotonin reuptake inhibitor (SSRI). If a patient is required to switch treatment due to lack of efficacy or intolerability, an alternative SSRI or newer generation, better tolerated antidepressant is suggested. At third-line of treatment CG90 guidelines recommend patients switch to an antidepressant of a different class (i.e. serotonin-norepinephrine reuptake inhibitors [SNRIs]), with tolerability issues including discontinuation symptoms a key decision maker in treatment (9). The comparators considered in this analysis were the SNRIs (duloxetine and venlafaxine). Additionally, agomelatine was included due to the availability of head-to-head data with vortioxetine. The results compared to the SSRIs (escitalopram, citalopram and sertraline) were also provided.

Data sources and clinical evidence

As no third-line data for vortioxetine were available, base case and scenario analyses were performed using several data sources in both the broad MDD population and patients who switched after

inadequate response (second-line). A detailed assessment of the data sets is provided in the supplementary material.

Discussion on the data sets

The systematic literature review associated with the Switch network (NICE TA367 submission [2015] and Brignone et al. [2014]) established that a limited number of RCT existed in a switch population (i.e. patients starting their second-line of treatment). (14) (22) Montgomery et al. (2014) (10) is a head-to-head trial of vortioxetine and agomelatine in switch patients [REVIVE] which established that vortioxetine had superior efficacy compared to agomelatine. Due to its design, REVIVE provides robust evidence for consideration in this cost-utility model. REVIVE was used as a starting point for the Switch network. This indirect treatment comparison provides comparative evidence focusing on the switch population. The results indicated that vortioxetine was more efficacious as measured by change from baseline symptom scores and response, in addition to better tolerability based on withdrawals due to AEs (statistically significant differences vs. sertraline, venlafaxine and bupropion). However, the heterogeneity within the included studies may limit the robustness of conclusions.

Llorca et al. (2014) (23) provided robust comparative evidence on the symptom score reductions (as measured by the change from baseline to 8 weeks on severity scales e.g. MADRS or HAM-D) and withdrawals due to AEs in the broad MDD population. The overall conclusion was the following, comparable efficacy between antidepressants and an advantage in tolerability for vortioxetine versus commonly used antidepressants. Secondary analyses on response and remission were also undertaken. However, these outcomes were not considered to be sufficiently robust as remission and response were not the primary efficacy endpoints in many of the studies that were included, and it was observed that these outcomes were not systematically reported in the publications

The analysis conducted in Pae et al. (2014) (24) included vortioxetine data from active reference and active comparator studies in broad MDD. In some of the placebo-controlled studies, an active reference was included as internal control. As acknowledged by the European Medicines Agency in the European Public Assessment Report, the exclusion of non-responders and the inclusion of previous responders in the active reference arm could have introduced a bias in favour of the efficacy

of the active reference. Therefore, differences in the efficacy of vortioxetine versus the active reference cannot be inferred on the basis of these studies. These results should be interpreted with caution. (25)

Wang et al. (2015) (26), a RCT comparing vortioxetine to venlafaxine in an Asian population [SOLUTION] was conducted in broad MDD. UK clinical experts stated that the relative effect is unlikely to differ between European and Asian populations. Non-inferiority in efficacy was concluded for vortioxetine compared to venlafaxine, however vortioxetine was associated with significantly fewer withdrawals due to AEs.

After comparison of the data sets, including strengths, weaknesses and results, the base case analyses assumed equivalent efficacy between treatments (based on estimates for vortioxetine from REVIVE) but incorporated the individual tolerability profiles of each antidepressant. This approach was aligned with the NICE appraisal conclusions, which stated that based on the total evidence, vortioxetine is likely to be of similar efficacy to other antidepressants in addition to a better overall tolerability profile. (14) Equivalent efficacy is further supported by NICE depression guidelines which concluded that generally antidepressants have largely equal efficacy. (9)

Model parameters

Efficacy and Tolerability parameters

The remission rate was taken from Montgomery et al. (2014) which provides evidence at second-line of treatment.(10) In order to adjust estimates to third-line, a proportionate reduction from second to third-line observed in STAR*D was applied to the vortioxetine absolute values for remission and no response (see supplementary material). As equivalent efficacy was considered, the values of 18.1% and 44.8% for remission and no response respectively were applied for all comparators in the model. The response rate of 37.1% was calculated as one minus the probability of remission and of no response (Table 1). The rates of withdrawal due AEs were subtracted directly from the proportion of patients in no response. This was validated by clinical opinion and an analysis of Montgomery et al. (2014) data which demonstrated that patients withdrawing due to AEs remained in the no response health state.

The efficacy values at 12 weeks were calculated based on conditional probabilities observed in the REVIVE study. Patients in the response health state at 8 weeks had a 59.92%, 32.14% and 8.33% probability of being in remission, response and no response at 12 weeks respectively (Table 1). These values were assumed to be applied to all comparators in the model due to lack of individual patient data for some comparators; and were consistent with the approach proposed by NICE. Similarly, relapse and remission at subsequent lines of treatment were also not considered to be treatment-specific, as observed in studies discussed by Limosin et al. (2004) and STAR*D respectively (4, 27).

Patients who achieve recovery face a two-month probability of recurrence (0.44%; See supplementary material for equations). This value was derived from a publication by Hardeveld et al. (2013). (28) The estimate was taken from a 10-year recurrence probability that was adjusted to reflect the two month cycles of the model.

Furthermore, spontaneous recovery was considered for the model. However, it was not included as it would require further assumptions, which would add complexity to the model and, at the same time, it would not change the overall conclusion of the study.

Table 1. Efficacy inputs

	Remission	No response	Response	Relapse	Recurrence
0 – 8 weeks					
3rd line	18.1%*	44.8%*^	37.1%¥	14.2%(27)	NA
			8 - 12 weeks		
3rd line	59.52%	32.14%	8.33%¥	14.2%(27)	NA
Switch lines					
4th line	13.0%(4)	NA	NA	25.0%	0.44%(28)
5th line	13.0%(4)	NA	NA	42.6%(4)	0.44%(28)
6th line	13.0%(4)	NA	NA	42.6%(4)	0.44%(28)

*Proportional reduction in efficacy from 2nd to 3rd line applied from STAR*D applied to REVIVE vortioxetine rates

^rates of withdrawals due to AEs subtracted from this.

¥ Response = 1 – remission – no response

Tolerability data for short-term events (Table 2) were retrieved from Montgomery et al. (2014) (10) for vortioxetine and agomelatine, and Cochrane reviews for the comparators sertraline (Cipriani et al. 2010) (29), citalopram (Cipriani et al. 2012) (30), escitalopram (Cipriani et al. 2009)(31) and duloxetine (Cipriani et al. 2012) (30). Long-term AEs (Table 2) occurring during the maintenance

phase were informed by Goodwin et al. (2009) (32) for agomelatine and Bet et al. (2013) (33) for sertraline, venlafaxine, citalopram, escitalopram and duloxetine. Pooled long-term extension studies provided the evidence for vortioxetine long-term AEs (34). Adverse-events were considered to be independent of each other. Therefore, patients could experience one or several AEs.

Table 2. Adverse event probabilities

	Vortioxetine	Agomelatine	Sertraline	Venlafaxine	Citalopram	Escitalopram	Duloxetine
Withdrawal due to AES[¥]	5.93%	9.50%	26.90%	28.20%	28.20%	28.20%	28.20%
Short-term							
Sexual dysfunction	0.40%	0.00%	10.64%	14.38%	6.24%	6.69%	3.77%
Dry mouth	4.74%	3.31%	14.45%	23.02%	6.68%	7.93%	15.00%
Nausea	16.21%	9.09%	26.17%	41.02%	10.99%	15.28%	30.27%
Sweating	2.37%	2.07%	13.34%	12.87%	6.50%	5.21%	8.85%
Somnolence	4.00%	7.85%	9.15%	8.58%	6.85%	6.56%	9.15%
Headache	10.28%	13.22%	26.08%	21.62%	10.85%	15.71%	15.59%
Diarrhoea	3.16%	3.31%	20.14%	8.95%	6.74%	8.33%	7.65%
Insomnia	7.10%	2.89%	18.10%	17.96%	7.46%	8.88%	12.30%
Dizziness	7.11%	11.57%	10.40%	13.24%	4.58%	5.34%	11.36%
Long term							
Sexual dysfunction	1.56%	0.00%	23.00%	31.00%	23.00%	23.00%	31.00%
Insomnia	3.50%	1.80%	7.00%	10.00%	7.00%	7.00%	10.00%
Weight gain	2.90%	0.00%	19.00%	17.00%	19.00%	19.00%	17.00%

[¥]Withdrawal due to AEs were subtracted from no response

Venlafaxine pooled Cochrane reviews

Utilities

Utility values (Table 3) for all efficacy health states were informed by applying the UK preference algorithm to the REVIVE EQ-5D data. (35) Disutilities were applied to the AEs and taken from Sullivan et al. (2004) (36) for all events except weight gain - this value was calculated based on information in Dixon et al. (2004). (37)

Table 3. Utilities according to health states and disutilities associated with adverse events

Utilities		**Value**
Acute phase 0-8 weeks	Depression at baseline	0.54
	Remission	0.85
	Response without remission	0.76
	No response	0.56
Acute phase 8-12 weeks	Remission	0.85
	Response without remission	0.76
	No response	0.56
Maintenance phase	Remission	0.85
	Response without remission	0.76
	Relapse	0.56
	Recovery	0.85
	Recurrence	0.56
Disutilities		
Short-term and long-term adverse events	Sexual dysfunction	0.049
	Headache	0.115
	Diarrhoea	0.044
	Somnolence	0.085
	Nausea	0.065
	Insomnia	0.129
	Dry mouth	0
	Dizziness	0
	Sweating	0
	Weight gain	0.032

Source utilities; REVIVE (10); disutilities: Sullivan 2004 (36)

The utility and disutility values are applied to the health states. These weights allow the Quality Adjusted Life Year (QALY) to be calculated. This is the main outcome of interest in this model and the measure of effectiveness.

Resource Use and Costs

An observational study (PERFORM) provided evidence for the resource use by health states in the acute phase in the UK.(38) However, it was not possible to differentiate between the UK resource use associated with remission and response as the response definition in PERFORM includes patients in

remission. This was also the case for the maintenance phase with data provided from Byford et al. (2011), the only identifiable UK source. (39) Therefore an assumption of equal resource use for response and remission was applied. This was considered to be a conservative approach, validated by expert opinion, as resource use may be underestimated for response. See supplementary material for detailed resource use data (Table 8). Unit costs (Table 4) were informed by the 2013 Personal Social Services Unit (PSSRU) and the National schedule of reference costs (40) (41). Finally, a discount rate of 3.5% was applied to both costs and outcomes in the second year.

Table 4. Resource use unit cost

Resource	Unit cost (£)
GP consultations	45
Psychiatrist consultations	125
Psychotherapy or counselling	145
Psychiatric ward admissions	342
General ward admissions	697
Accident & emergency visits	177

Source: 2013 Personal Social Services Unit (PSSRU) and the National schedule of reference costs (40) (41)

Analyses

The results of the model were presented based on the Incremental Cost Effectiveness Ratio (ICER). It is the difference in cost divided by the difference in effect (QALY) between two treatments. In the UK, an acceptable cost-effectiveness threshold considered by NICE is £20,000 – £30,000/QALY. This is the cost the UK NHS are willing to pay for an additional QALY gained. Scenario analyses were conducted to reflect the uncertainty in model structure, duration of maintenance phase and the setting of care. The maintenance phase was further investigated in a scenario of 22 months. This was based on UK guidelines (NICE CG90 and BAP) which have stated high risk patients (e.g. more than 5 lifetime episodes and/or 2 episodes in the last few years) should receive treatment for up to 2 years. (9) (19) Additionally, an analysis considering management in secondary care was considered by assuming that all patients were initially treated by a psychiatrist and not a GP. A probabilistic sensitivity analysis (PSA) was performed to test the robustness of the results.

Results

The ICERS based on pairwise analyses versus vortioxetine, and incremental ICERs are presented in

Treatments	Total cost	Total QALYs	Δ Cost	Δ QALY	ICER (vortioxetine vs. comparator)	Δ ICERS (Including SSRIs; QALY)	Δ ICERS (Excluding SSRIs; QALY)	Probability of vortioxetine CE at λ = £20,000	Probability of vortioxetine CE at λ = £30,000
Base case: Equivalent efficacy									
Citalopram	£1,342	1.414	Ref	Ref	£4,590	Reference	n/a	63%	65%
Escitalopram	£1,347	1.414	£5	-0.001	£3,956	Dominated	n/a	62%	65%
Sertraline	£1,357	1.412	£10	-0.002	£2,746	Dominated	n/a	65%	67%
Vortioxetine	£1,399	1.427	£42	0.015	Reference	£4,590	Reference	Reference	Reference
Venlafaxine	£1,400	1.410	£1	-0.017	Dominant	Dominated	Dominated	65%	67%
Duloxetine	£1,549	1.411	£149	0.002	Dominant	Dominated	Dominated	72%	72%
Agomelatine	£1,567	1.428	£19	0.016	£243,079*	£243,079*	£243,079*	52%	52%
Montgomery et al. (2014)									
Vortioxetine	£1,399	1.427			Reference	n/a	Reference	Reference	Reference
Agomelatine	£1,690	1.380	£291	-0.047	Dominant	n/a	Dominated	98%	98%

Table 5. The base case analysis of equivalent efficacy demonstrated that vortioxetine was a cost-effective treatment option versus citalopram (ICER=£4,590), escitalopram (ICER=£3,956) and sertraline (ICER=£2,746). In the comparison with venlafaxine and duloxetine, vortioxetine was a dominant strategy as it was associated with increased QALYs at a lower cost. Agomelatine had an ICER of £243,079 versus vortioxetine, which is substantially above the NICE threshold and therefore cannot be considered a cost-effective option according to these criteria. Additionally, results based on robust head-head evidence in a switch population demonstrated that vortioxetine was a dominant strategy versus agomelatine.

According to UK guidelines, a treatment with a different mechanism of action should be considered at third-line. Therefore, the results excluding SSRIs provided further evidence for the cost-effectiveness of vortioxetine as a third-line of treatment due to its dominance over venlafaxine and duloxetine.

Treatments	Total cost	Total QALYs	Δ Cost	Δ QALY	ICER (vortioxetine vs. comparator)	Δ ICERS (Including SSRIs; QALY)	Δ ICERS (Excluding SSRIs; QALY)	Probability of vortioxetine CE at λ = £20,000	Probability of vortioxetine CE at λ = £30,000
Base case: Equivalent efficacy									
Citalopram	£1,342	1.414	Ref	Ref	£4,590	Reference	n/a	63%	65%
Escitalopram	£1,347	1.414	£5	-0.001	£3,956	Dominated	n/a	62%	65%
Sertraline	£1,357	1.412	£10	-0.002	£2,746	Dominated	n/a	65%	67%
Vortioxetine	£1,399	1.427	£42	0.015	Reference	£4,590	Reference	Reference	Reference
Venlafaxine	£1,400	1.410	£1	-0.017	Dominant	Dominated	Dominated	65%	67%
Duloxetine	£1,549	1.411	£149	0.002	Dominant	Dominated	Dominated	72%	72%

Agomelatine	£1,567	1.428	£19	0.016	£243,079*	£243,079*	£243,079*	52%	52%
Montgomery et al. (2014)									
Vortioxetine	£1,399	1.427			Reference	n/a	Reference	Reference	Reference
Agomelatine	£1,690	1.380	£291	-0.047	Dominant	n/a	Dominated	98%	98%

Table 5. Base case results

* ICERs are based on lower cost and fewer QALYs for vortioxetine, so the ICERs should be interpreted as willingness to accept QALYs lost, not willingness to pay for QALYs gained.
ICER: Incremental cost effectiveness ratio; QALY: quality adjusted life years; SSRI: selective serotonin reuptake inhibitor; CE: cost effectiveness; λ = threshold; Δ = incremental

Further details on the results of the scenario analyses can be found in the supplementary material. In a scenario considering the management of patients in secondary care, the cost doubled for all treatments, with QALYs remaining the same. This was due to an increase in psychiatrist visits compared to GP visits and therefore the associated healthcare cost. In this scenario, vortioxetine became the least costly treatment option compared to a ranking of fourth in the base case analyses. This resulted in a dominant ICER against all comparators except for agomelatine. However, the ICER for agomelatine compared to vortioxetine showed it not to be a cost-effective treatment option at £332,296.

An extension of the maintenance phase of treatment to 22 months resulted in total costs increasing for all treatments due to greater drug acquisition costs and an increased risk of long-term AEs, as patients received treatment for longer in this scenario. The total QALYs gained generally decreased as long-term adverse events were increasing as well as the cumulative risk of relapse. In this scenario, vortioxetine was proportionally more expensive than venlafaxine compared to the base case but the ICER was considerably below the NICE threshold at £8,846/QALY. The scenario where care is conducted within a secondary care setting during the 22-month maintenance phase did not change the ranking of the cost-utility results compared to management in primary care.

The probabilistic sensitivity analysis (PSA) which explores the robustness in the results demonstrated that vortioxetine was likely to be cost-effective versus all comparators at a NICE cost/QALY threshold ranging from £20,000 to £30,000. It had the highest likelihood of cost-effectiveness versus duloxetine (72%; Table 3), followed by a probability of around 60-70% versus citalopram, escitalopram, sertraline, and venlafaxine, and just over 50% compared to agomelatine. Using data from Montgomery 2014, vortioxetine had a 98% probability of being cost-effective versus agomelatine. See supplementary material for cost-effectiveness planes.

Discussion

Economic evaluations play an important role in identifying cost-effective treatments in depression due to its chronic nature and significant resource burden (42) (43).

Vortioxetine has been recently approved by NICE as an option for treating MDE in adults whose condition has responded inadequately to two antidepressants within the current episode. The base case pair-wise analyses showed vortioxetine to be a cost-effective treatment versus citalopram, escitalopram and sertraline when a NICE threshold of £20,000 - £30,000/QALY was considered. Vortioxetine was a dominant strategy versus venlafaxine and duloxetine. For the comparison to agomelatine, the base case analysis led to an ICER of £243,079 versus vortioxetine. The results based on Montgomery et al. (2014), demonstrated that vortioxetine had a 98% probability of being cost-effective versus agomelatine at a threshold of £20,000/QALY. These results are considered particularly robust as they are based on data from a head-to-head study.

This economic model has been adapted from a previously published model conducted in switch patients in Finland and an overall MDD population in South Korea.(44) (45) In the Finnish analyses Vortioxetine was found to be a dominant treatment option versus agomelatine, sertraline and venlafaxine. Similarly, this was the case in the South Korean model with dominance observed versus venlafaxine at first-line and agomelatine at second-line. The model discussed herein was consistent with these results in terms of comparisons with venlafaxine and agomelatine (when REVIVE data were considered). Vortioxetine was not a dominant treatment option versus sertraline, but it was still considered to be cost-effective.

An economic evaluation has been undertaken in Scotland comparing venlafaxine and duloxetine, the two treatments of interest to the decision problem, (Benedict et al. 2010).(46) The model evaluates a population who failed on first line SSRI. The analysis considers similar health states and corresponding utilities (response: 0.68, remission: 0.79, no response: 0.55). In Benedict et al. (2010), duloxetine is associated with lower costs and greater QALYs compared to venlafaxine. The improved health gains for duloxetine are observed in the model discussed herein, but the costs are higher. Caution should be taken when comparing the results of the model. This is due to the different population of interest, longer time horizon, and the non-inclusion of tolerability and AEs in Benedict's model. However, the range of cost-effectiveness is similar to results presented, with ICERs below £7,000/QALY.

The main updates in the structure of the model were the inclusion of response, considering recurrence after recovery, the extension of the acute phase to 3 months, and the change in the time horizon from 12 to 24 months. The updated structure was informed by a model presented in Trivedi et al. (2004) (17), in addition to a comprehensive review of UK guidelines and validation by clinical experts. This ensured applicability to the UK setting and the decision question of positioning in third-line. However, these changes have required some assumptions, particularly related to the data inputs.

It is also of great interest to consider the scenarios comparing primary and secondary care management, and the length of the maintenance phase (6 and 22 months) in the UK. Vortioxetine appears the cheapest treatment when considering the management of patients within secondary care. This can be explained by a better tolerability profile for vortioxetine leading to fewer patients switching and thus avoiding the higher costs associated with management. According to UK clinical guidelines, patients with a higher risk of relapse should continue on treatment for at least two years. The results of the extended 22-month maintenance phase scenario provide evidence for vortioxetine as a cost-effective treatment option in this group of patients.

NICE CG90 guidelines have highlighted the importance of having an antidepressant model that is comprehensive in its approach (9). Adverse events were not considered in the NICE model, this was also the case for many previously published models.(1, 46) The inclusion of safety and tolerability within MDD economic models is important, as patient's safety when choosing treatment should be one of the primary considerations. While equivalent efficacy was considered between all treatments, the withdrawal due to AEs and tolerability had an important influence on the results. The lower withdrawal rates for vortioxetine compared to venlafaxine and duloxetine (5.93%, 28.20% and 28.20% respectively) support clinical opinion on the selection of treatments with more favourable tolerability profiles for patients who have not tolerated previous antidepressants.

Limitations

Although the favourable tolerability of vortioxetine has been reflected in the model to some extent, not all implications could be included. For example, the impact on decreased compliance to treatment, and premature cessation of treatment on clinical outcomes such as recurrence, have not been considered. In addition, the relative lack of discontinuation symptoms associated with vortioxetine compared to other antidepressants apart from agomelatine (Taylor et al. 2015) have not been

included in terms of either their impact on HRQoL or decrease in follow-up consultations where close monitoring of down-titration is necessary (47).

Furthermore, a patient's profile, previous treatment history including side-effects, and patient preference, determines the choice of suitable treatment options. Consequently, at later treatment lines the number of appropriate comparators will decrease. Explicitly modelling this proves challenging without increasing uncertainty in the results due to the vast number of additional assumptions required to support this.

In MDD, a strict treatment pathway is unlikely to provide the optimal treatment strategy for this large and highly heterogeneous patient population. When choosing appropriate treatments, clinicians give consideration to individual treatment and patient profiles, including factors such as a patient's previous treatment experience and preferences. Many of these aspects merit the consideration of vortioxetine with its different mode of action, and favourable safety and tolerability which are likely to translate into clinical and economic benefits for patients who have switched treatment.

Conclusion

Vortioxetine is an antidepressant with a unique mechanism of action. It has been shown to be at least as efficacious, and generally better tolerated, than other antidepressants in MDD. This has been observed consistently in the full MDD population through both direct head-to-head and indirect evidence. The model developed is a relatively accurate representation of the management of patients with recurrent MDD in the UK. The results of the base case analysis indicated that vortioxetine, with its tolerability benefits, is expected to be a cost-effective treatment option for patients experiencing an MDE after inadequate response to at least two previous antidepressants in the UK. The results of the study should be interpreted in light of the assumptions required for missing data on comparative effectiveness. These results are robust to the changes employed in scenario analyses conducted around treatment in both primary and secondary care, and length of maintenance treatment.

Acknowledgements

The authors would like to thank Jack Ziomek, Mapi Group, London, UK, for his contribution in developing this manuscript.

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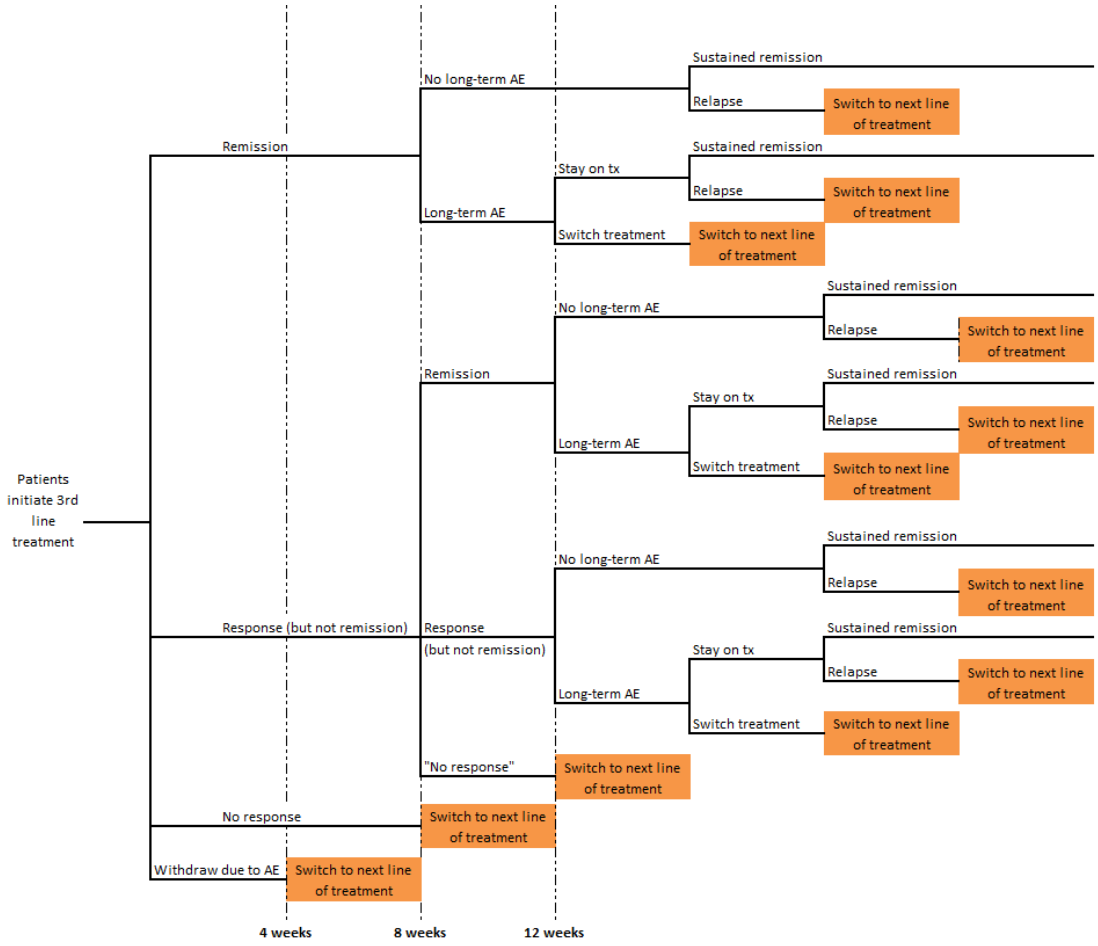
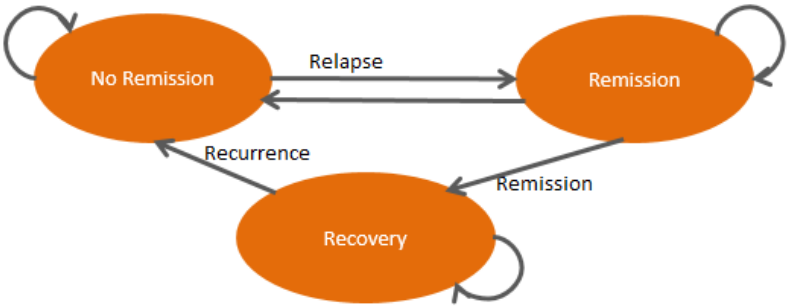
Figure 1. Model structure





Supplementary material

Figure 2S. Vortioxetine vs. venlafaxine (equivalent efficacy)

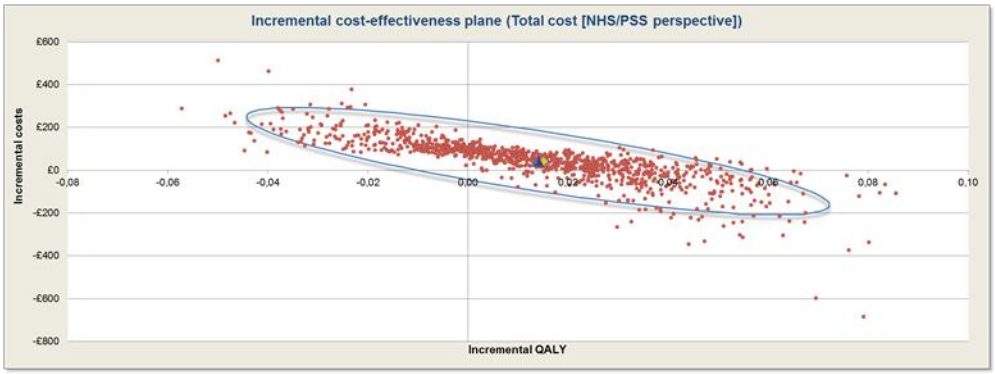


Figure 3S. Vortioxetine vs. duloxetine (equivalent efficacy)

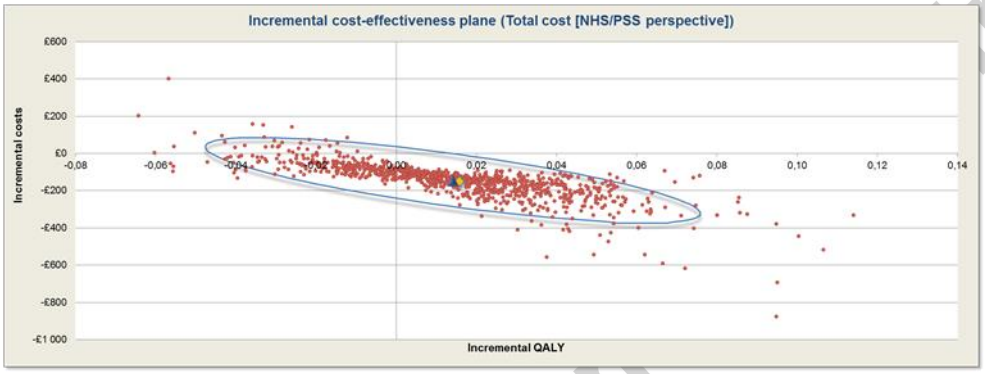
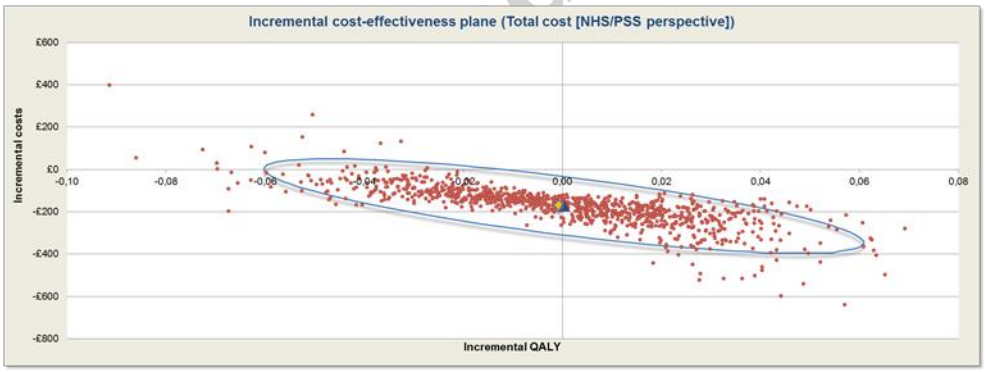


Figure 4S. Vortioxetine vs. agomelatine (equivalent efficacy)



Supplementary Material

To allow for comparison across all the studies, the relevant results were presented based on odds ratios (OR) using vortioxetine as the reference.

Table 6S. Comparison of data sources

	Montgomery et al. (2014) (10) ¥	**Switch Network (NICE submission; 2015) (14, 15)** ¥	**Llorca et al. (2014) (23)**	**Pae et al. (2015) (24)**	**Wang et al. (2015) (26)**
Description of the data source					
Main objective of the study	This randomised, double-blind, 12-week study compared efficacy and tolerability of flexible-dose treatment with vortioxetine (10–20 mg/day) versus agomelatine (25–50 mg/day) in MDD patients with inadequate response to SSRI/SNRI monotherapy	To assess the relative efficacy and tolerability of vortioxetine against different antidepressant monotherapies in patients with MDD with inadequate response to SSRI or SNRI therapy.	Indirect Comparisons of efficacy and tolerability between active treatments and vortioxetine using meta-regression in MDD patients	A meta-regression in short-term vortioxetine trials to assess the efficacy, discontinuation rate and side effects in MDD patients	This randomized, double-blind 8 week study compared the efficacy and tolerability of fixed-dose treatment with vortioxetine (10 mg/day) and venlafaxine extended release (XR) (150 mg/day) in MDD patients
Population	MDD patients with inadequate response to SSRI or SNRI	MDD patients with inadequate response to SSRI or SNRI	MDD patients	MDD patients	MDD patients
Methods	Randomised Controlled Trial	Indirect treatment comparisons (Bucher method)	Indirect treatment comparisons (meta-regression)	Meta-analysis	Randomised Controlled Trial
Primary outcomes in the data source	Efficacy: Change from baseline to week 8 in MADRS total score Tolerability: Withdrawal due to AEs	Efficacy: Remission Tolerability: Withdrawal due to adverse events	Efficacy: Standardized mean difference in change from baseline to 2 months on primary endpoint [MADRS/HAM-D]) Tolerability: withdrawal rate due to adverse events.	Efficacy: Mean change from baseline on MADRS/HAM-D Tolerability: withdrawal due to AEs	Efficacy: Change from baseline to week 8 in MADRS total score Tolerability: Withdrawal due to AEs
Time point of assessment	8 weeks	8 weeks	8 weeks	12 weeks	8 weeks

	Montgomery et al. (2014) (10)¥	Switch Network (NICE submission; 2015) (14, 15)¥	Llorca et al. (2014) (23)	Pae et al. (2015) (24)	Wang et al. (2015) (26)
Input data used in the CEA					
Efficacy parameters – Remission					
Remission definition (Study measure)	MADRS total score (%)	A score of ≤7 on the HAM-D scale or ≤10 on the MADRS (Relative difference)	SMD in change from baseline to 2 months on primary endpoint [MADRS/HAM-D] (SMD)	A score of ≤7 on the HAM-D scale or ≤10 on the MADRS (OR)	MADRS total score (%)
Remission rates					
Vortioxetine	Reference (OR)*	Reference (OR)*	Reference (OR)*	Reference (OR)*	Reference (OR)*
Agomelatine	1.63 [95% CI: 1.12; 2.37]	1.63 [95% CI: 1.12; 2.37]	1.20 (p=0.470)	0.84 [95% CI: 0.58; 1.24]	NA
Venlafaxine	NE	1.26 [95% CI: 0.52; 3.07]	0.69 (p=0.444)		1.07 [95% CI: 0.73; 1.57]
Duloxetine	NE	NE	0.89 (p=0.526)		NE
Escitalopram	NE	NE	0.99 (p=0.981)	NE	NE
Citalopram	NE	1.98 [95% CI:0.59; 6.60]	NE	NE	NE
Sertraline	NE	1.94 [95% CI: 0.90; 4.20]	NE	NE	NE
Tolerability parameters – Withdrawal rates due to adverse events					
Withdrawal rates due AEs (Study measure)	%	Risk difference	OR	OR	OR
Vortioxetine	Reference (OR)**	Reference (OR)**	Reference (OR)**	Reference (OR)**	Reference (OR)**
Agomelatine	0.60 [95% CI: 0.31; 1.18]	0.60 [95% CI: 0.31; 1.18]	1.77 (p=0.03)	0.73 [95% CI: 0.55; 0.96]	NA
Venlafaxine	NE	0.16 [95% CI: 0.4; 0.76]	0.47, (p=0.01)		0.43 [95% CI; 0.22; 0.83]
Duloxetine	NE	NE	0.75 (p=0.26)		NE
Escitalopram	NE	NE	0.67 (p=0.28)	NE	NE
Citalopram	NE	0.15 [95% CI: 0.02;0.86]	NE	NE	NE
Sertraline	NE	0.17 [95% CI: 0.04;0.73]	NE	NE	NE

AEs: Adverse events; HAM-D: Hamilton Depression Rating Scale; MDD: Major Depressive Disorder; MADRS: Montgomery-Asberg Depression Scale; NE: Not evaluated; OR: Odds Ratio; SMD: Standard mean difference; SNRI: serotonin–norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor

¥ Montgomery et al. (2014) was the starting point for the Switch Network

*Odds ratio >1 favours vortioxetine

**Odds ratio <1 favours vortioxetine

Table 7S. Adjustment to third-line based on STAR*D

Line	Remission probability		No response (1-response) probability	
	STAR*D	REVIVE – vortioxetine	STAR*D	REVIVE – vortioxetine
2nd	30.6%	40.5%	71.5%	38.5%
3rd	13.7%	18.13%*	83.2%	44.8%*

*Proportional reduction in efficacy from second to third-line applied from STAR*D.

Equation 1S. Calculating the one-month relapse rate

$$-[\ln(1-23.20\%)]/120\ months = 0.0022$$

Equation 2S. Converting the relapse rate to a two-month probability

$$1 - EXP(-0.0022 * 2) = 0.439\%$$

Table 8S. Health care resource utilisation by health state

Healthcare resource utilization		No. of visits	Patients with ≥1 visit (%)	Source
GP consultations	Remission 0-8 weeks	**2.50**	100.0%	PERFORM (38)
	No response 0-8 weeks	**2.80**	100.0%	PERFORM (38)
	Response 0-8 weeks	**2.50**	100.0%	Assumed equivalent to remission
	Remission 8-12 weeks	***1.25***	100.0%	Calculation
	Response 8-12 weeks	***1.25***	100.0%	Assumed equivalent to remission
	No response 8-12 weeks	***1.40***	100.0%	Calculation; assumption
	Remission after 12 weeks	**2.15**	100.0%	Byford et al. 2011(39)
	Response after 12 weeks	**2.15**	100.0%	Assumed equivalent to remission
	Relapse after 12 weeks	**2.89**	100.0%	Byford et al. 2011 (39)
Psychiatrist consultations	Remission 0-8 weeks	**0.00**	0.0%	PERFORM (38)
	No response 0-8 weeks	**1.00**	1.3%	PERFORM (38)
	Response 0-8 weeks	**0.00**	0.0%	Assumed equivalent to remission
	Remission 8-12 weeks	***0.00***	0.0%	Calculation; assumption
	Response 8-12 weeks	**0.00**	0.0%	Assumed equivalent to remission
	No response 8-12 weeks	***0.50***	1.3%	Calculation; assumption
	Remission after 12 weeks	**0.23**	2.9%	Byford et al. 2011 (39)
	Response after 12 weeks	**0.23**	2.9%	Assumed equivalent to remission
	Relapse after 12 weeks	**0.23**	5.0%	Byford et al. 2011 (39)
Psychotherapy or counselling	Remission 0-8 weeks	**1.20**	12.7%	PERFORM (38)
	No response 0-8 weeks	**2.10**	18.8%	PERFORM (38)
	Response 0-8 weeks	**1.20**	12.7%	Assumed equivalent to remission
	Remission 8-12 weeks	***0.60***	12.7%	Calculation; assumption
	Response 8-12 weeks	**0.60**	12.7%	Assumed equivalent to remission
	No response 8-12 weeks	***1.05***	18.8%	Calculation; assumption
	Remission after 12 weeks	**0.00**	0.2%	Byford et al. 2011 (39)
	Response after 12 weeks	**0.00**	0.0%	Assumed equivalent to remission
	Relapse after 12 weeks	**0.00**	0.2%	Byford et al. 2011 (39)

		Mean number of days	Patients with ≥1 visit by ward (%)	
Psychiatric ward admissions	Remission 0-8 weeks	**0.00**	0.0%	PERFORM (38)
	No response 0-8 weeks	**0.00**	0.0%	PERFORM (38)
	Response 0-8 weeks	**0.00**	0.0%	Assumed equivalent to remission
	Remission 8-12 weeks	***0.00***	0.0%	Calculation; assumption
	Response 8-12 weeks	**0.00**	0.0%	Assumed equivalent to remission
	No response 8-12 weeks	**0.00**	0.0%	Calculation; assumption
	Remission after 12 weeks	**0.22**	5.2%	Byford et al. 2011 (39)
	Response after 12 weeks	**0.22**	5.2%	Assumed equivalent to remission
	Relapse after 12 weeks	**0.23**	5.7%	Byford et al. 2011 (39)
General ward admissions	Remission 0-8 weeks	**0.00**	0.0%	PERFORM (38)
	No response 0-8 weeks	**0.00**	0.0%	PERFORM (38)
	Response 0-8 weeks	**0.00**	0.0%	Assumed equivalent to remission
	Remission 8-12 weeks	***0.00***	0.0%	Calculation; assumption
	Response 8-12 weeks	**0.00**	0.0%	Assumed equivalent to remission
	No response 8-12 weeks	**0.00**	0.0%	Calculation; assumption
	Remission after 12weeks	**0.00**	0.0%	Assumed equivalent to acute phase
	Response after 12 weeks	**0.00**	0.0%	Assumed equivalent to remission
	Relapse after 12 weeks	**1.00**	0.5%	Assumed equivalent to acute phase
Accident & Emergency visits	Remission 0-8 weeks	**0.00**	0.0%	PERFORM (38)
	No response 0-8 weeks	**0.00**	0.0%	PERFORM (38)
	Response 0-8 weeks	**0.00**	0.0%	Assumed equivalent to remission
	Remission 8-12 weeks	***0.00***	0.0%	Calculation; assumption
	Response 8-12 weeks	**0.00**	0.0%	Assumed equivalent to remission
	No response 8-12 weeks	**0.00**	0.0%	Calculation; assumption
	Remission after 12 weeks	**0.22**	3.1%	Byford et al. 2011 (39)
	Response after 12 weeks	**0.22**	3.1%	Assumed equivalent to remission
	Relapse after 12 weeks	**0.25**	3.3%	Byford et al. 2011 (39)

Table 9S. Scenario results

Treatments	Total cost	Total QALYs	ICER (vortioxetine vs. comparator)	Incremental ICERS (Including SSRIs; QALY)	Incremental ICERS (Excluding SSRIs; QALY)
Scenario 1: Patients managed in secondary care (Equivalent efficacy)					
Vortioxetine	£3,033	1.427	Reference	Reference	Reference

Citalopram	£3,073	1.414	Dominant	Dominated	n/a
Escitalopram	£3,079	1.414	Dominant	Dominated	n/a
Sertraline	£3,088	1.412	Dominant	Dominated	n/a
Venlafaxine	£3,135	1.410	Dominant	Dominated	Dominated
Agomelatine	£3,263	1.428	£332,296*	£332,296*	£332,296*
Duloxetine	£3,284	1.411	Dominant	Dominated	Dominated
Scenario: Patients managed in secondary care (Montgomery)					
Vortioxetine	£3,033	1.427	Reference	n/a	Reference
Agomelatine	£3,572	1.380	Dominated	n/a	Dominated
Scenario 2: Maintenance treatment up to 22 months and primary care (Equivalent efficacy)					
Citalopram	£1,659	1.408	£22,664	Reference	n/a
Escitalopram	£1,670	1.407	£20,628	Dominated	n/a
Sertraline	£1,682	1.405	£16,763	Dominated	n/a
Venlafaxine	£1,778	1.403	£8,846	Dominated	Ref
Vortioxetine	£1,923	1.419	Reference	£22,664	£8,846
Duloxetine	£2,184	1.404	Dominant	Dominated	Dominated
Agomelatine	£2,316	1.420	£700,807*	£700,807	£700,807
Scenario: Maintenance treatment up to 22 months and primary care (Montgomery)					
Vortioxetine	£1,923	1.419	Reference	n/a	Reference
Agomelatine	£2,237	1.373	Dominant	n/a	Dominated
Scenario: Maintenance treatment up to 22 months and secondary care (Equivalent efficacy)					
Citalopram	£3,908	1.408	£18,616	Reference	n/a
Escitalopram	£3,918	1.407	£16,787	Dominated	n/a
Sertraline	£3,931	1.405	£13,522	Dominated	n/a
Venlafaxine	£4,021	1.403	£6,289	Dominated	Reference
Vortioxetine	£4,124	1.419	Reference	£18,616	£6,289
Duloxetine	£4,428	1.404	Dominant	Dominated	Dominated
Agomelatine	£4,584	1.420	£827,762*	£827,762	£827,762
Scenario: Maintenance treatment up to 22 months and secondary care (Montgomery)					
Vortioxetine	£4,124	1.419	Reference	n/a	Reference
Agomelatine	£4,543	1.373	Dominant	n/a	Dominated

Highlights

- Limited guidance exists for management of third-line patients with depression
- The model accounts for management of depression, including inadequate response
- Vortioxetine is efficacious, and has a favourable safety profile vs comparators
- Vortioxetine proved to be a cost-effective treatment vs other antidepressants