The Impact of Premature Discontinuation of Antidepressant Therapy in Major Depressive Disorder in the UK

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Abstract

OBJECTIVE: Antidepressant therapy is highly effective in patients with major depressive disorder (MDD). Evidence has shown that most patients stay on pharmacotherapy for less than 6 months even though clinical guidelines recommend treatment for longer periods of time. The objective of this study was to assess the impact of premature discontinuation of antidepressant therapy on costs and outcomes in MDD patients.

METHODS: We created a UK adaptation of a simulation model to compare the costs and outcomes associated with patients who respond to treatment with a selective serotonin reuptake inhibitor (SSRI) and discontinue treatment prematurely to those who respond to SSRIs and complete the recommended course of treatment. Patients are outpatients and are assumed to follow treatment as recommended by the clinical guidelines except when early discontinuation occurs. The model considers medication, primary care physician visit, specialist (i.e., psychiatrist, hospital days, suicide, etc.), and adverse event costs. Treatment efficacy was taken from published meta-analyses, and early discontinuation was estimated from the published literature. Resource use was estimated from the clinical guidelines and published literature. Unit costs were drawn from standard published sources and inflated to 2003 UK pounds.

RESULTS: Over the course of 5 years, we observe that continuation patients (i.e., patients who complete a recommended course of treatment) have 73 fewer symptom days, 9 fewer disability days, and lower costs by $287 than discontinuation patients (i.e., patients who discontinue early) when having relapses/recurrences. In the index episode, continuation patients incur more costs than discontinuation patients due to increase usage of drugs and physician. However, patients who discontinue incur more costs later due to higher relapse/recurrence rates.

CONCLUSION: By encouraging patients to complete a full course of drug therapy, patients will incur fewer costs and fewer symptom and disability days.

Background

Depression is the most common mental illness and represents a pervasive health problem. There were an estimated 2.6 million cases of treated clinical depression in England for 2000 (Thomas et al., 2003) based on the 1998 Office of National Statistics (ONS) estimated prevalence rates (29.0 per 1000 male; 70.1 per 1000 female). Direct treatment costs of depression in the UK as a whole have been estimated at £370 billion per year (Thomas et al., 2003), with an estimate of overall cost burden at around £9 billion.

Treatment for MDD is highly successful, although fewer than half of those suffering from MDD actually seek treatment (Rupp et al., 1998). The majority of major depression sufferers who do seek treatment approach their primary care physicians (PCPs) (Anderson, 2000). When patients seek treatment, evidence has shown that the majority of patients stay on pharmacotherapy for less than 6 months even though the treatment guidelines recommend treatment for longer periods of time (Anderson, 2000).

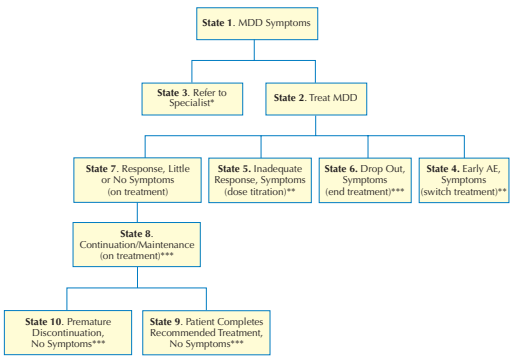
In this analysis, we compare the costs and outcomes associated with patients treated in the primary care setting who respond to therapy and discontinue treatment prematurely to those who respond to therapy and complete the recommended course of treatment.

Methods

To perform this analysis, we constructed a simulation model as presented in Figure 1.

- Patients are assumed to be treated with a selective serotonin reuptake inhibitor (SSRI) and to follow treatment as recommended by the clinical guidelines.
- Patients who fail to respond to the index SSRI are assumed to be treated subsequently with another SSRI in which clinical outcomes are similar.

Figure 1. Model Structure



- Patients progress from one state to another based on data primarily from meta-analyses published in the medical literature (Table 1).
- The time a patient spends and the average number of physician visits incurred in each health state varies depending upon the state and patient attributes. These values were based on data from the clinical guidelines.

Table 1. Clinical Inputs

Parameter	Value	Source/Assumption
Placebo response rate	32%	Williams et al. (2000)
Relative risk of response	1.6	Williams et al. (2000)
Discontinue due to AEs	8.0%	Williams et al. (2000)
Drop out due to lack of efficacy	5.3%	Williams et al. (2000)
Placebo relapse/recurrence rate	60.8%	Williams et al. (1999) adjusted to 1 year
Relative risk of relapse/recurrence	0.723	Reimherr et al. (2001)
Increased risk of relapse/ recurrence while not on antidepressant	1.77	Melfi et al. (1998)
Average number of disability days lost during an episode	3.67 per 30 day period	Broadhead et al. (1990)
Average number of disability days lost while not experiencing symptoms	0.66 per 30 day period	Broadhead et al. (1990)

Methods *(continued)*

- The model very closely follows the Department of Veterans Affairs, Medical Advisory Panel for the Pharmacy Benefits Management Strategic Health Group's (PBMSHG) treatment algorithm.
- The model follows guidelines endorsed by the American Psychiatric Association (2000), the Agency for Health Care Policy and Research (AHCPR, 1994) and the British Association of Psychopharmacology (Andersen et al., 2000).

Model Assumptions

- Patients progress through the model for an index and relapse/recurrence (if it occurs) episode of depression.
- Patients without a relapse/recurrence within 5 years are assumed to not have future episodes and thus incur no more costs and symptom days.
- Patients referred to a specialist for the relapse/recurrence episode incur costs and outcomes for 1 more year after referral. As a result, costs and outcomes could be understated for these patients.
- As in the clinical trials, patients are assumed to have had at least two prior episodes of depression and are treated with an SSRI.
- Continuation patients are assumed to respond to the index therapy with an SSRI. These patients stay on the index treatment until they complete the recommended course of pharmacotherapy. Continuation therapy in the model is assumed to last 9 months (270 days).
- Discontinuation patients are assumed to respond to the index therapy with SSRI; however, they are assumed to discontinue pharmacotherapy after 141 days ([(13%/30%) * 3 months + (17%/30%) * 6 months] * 30 days = 141 days; unpublished analysis of ARTIST data reported by Williams, 2003).
- For patients who complete the recommended course of treatment, the probability of relapse/recurrence is assumed to be equal to the relapse/recurrence rate observed by patients on drug in the clinical trials.
- For patients who discontinue early, the probability of relapse/recurrence is assumed to be equal to 1.77 times the observed probability of relapse/ recurrence in the clinical trials (Melfi et al., 1998).
- Patients who have a relapse/recurrence are treated with the same drug as in the previous treatment; however, this time they may also incur other clinical outcomes (e.g., referral to a specialist, early adverse event, inadequate response to treatment, or drop out of treatment).

Resource Use/Unit Costs

The resource use in treating MDD in the primary care setting results primarily from visits to the PCP and antidepressant use. Cost data used in the model are summarized in Table 2.

Table 2. Resource Use/Costs

Resource	Unit Cost	Source/Assumption
Physician visit–outpatient mental health	£114.21	NHS Trust Financial returns
General practitioner	£27.00	PSSRU unit costs of health and social care
Inpatient psychiatric hospital stay for ICD-10 F32 (depressive episode)	£165.00	PSSRU unit costs of health and social care
SSRI cost per day (starting dose of 20 mg/day)	£0.25	Based on generic fluoxetine (BNF, 2003)
SSRI cost per day (titrated dose of 40 mg/day)	£0.51	Based on generic fluoxetine (BNF, 2003)
Suicide attempt	£567.42	Almond et al. (2000)
Suicide completion	£189.14	Almond et al. (2000)
Costs are inflated to 2003 values using the health service cost index (HSCI).		

- The costs of treating adverse events (AEs) are estimated as a weighted average of the expected incidence and cost of treating each AE.
- Psychotherapy is not considered as a treatment option.
- All costs are reported in 2003 UK £ and discounted using a rate of 6% for both costs and outcomes.

Results

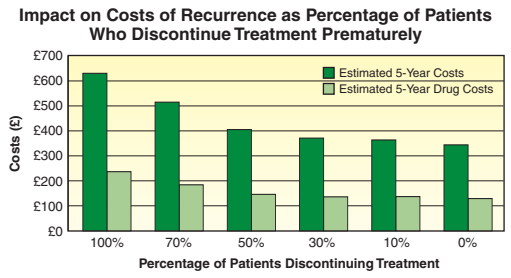
Table 3. Summary of Results

Parameter	Discontinuation Patients	Continuation Patients
Symptom Days	166.8	94.0
Disability Days	20.4	11.5
Drug Costs in Initial Episode	£90.07	£148.46
Drug Costs in Relapse/ Recurrence Episode	£109.39	£75.81
Total Costs	£630.89	£344.26

- Patients who continue therapy as recommended by the treatment guidelines are better maintained. While they incur higher drug and physician costs in the initial episode, as relapse/recurrences occur their costs decrease as a result of this maintenance.
- Costs incurred by patients who discontinue treatment prematurely are almost twice those incurred by patients who stay on therapy for the recommended course.
- Disability days experienced by patients who discontinue treatment prematurely are approximately 1.8 times more than those experienced by patients who stay on therapy for the recommended course.

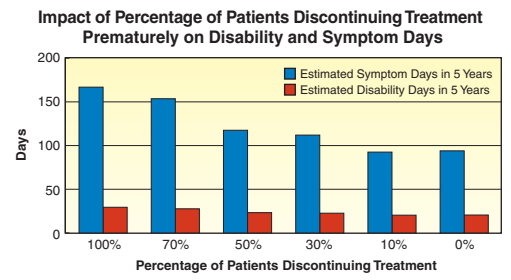
Results *(continued)*

Figure 2. Impact to Payers



- As the percentage of patients who discontinue treatment prematurely increases, the costs to the national health service increase.

Figure 3. Impact to Employers



- As the percentage of patients who discontinue treatment prematurely increases, the number of anticipated disability days increases.
- As the percentage of patients who discontinue treatment prematurely increases, drug costs remain at about 1/3 of total costs
- As the percentage of patients who discontinue treatment prematurely increases, disability days occur in about 17%–20% of symptom days.

Conclusions

Patients who continue maintenance therapy may incur higher drug and physician visit costs in the initial episode. However, their costs decrease over time. Thus, the national health service, employers, and patients will experience benefits in terms of fewer costs and fewer symptom and disability days when patients continue drug therapy.

References

Agency for Health Care Policy and Research (AHCPR). Depression in primary care: Volume 2 – Treatment of Major Depression, Clinical Practice Guideline Number 5. November 18, 1994.

Almond S, O'Donnell O. Cost analysis of the treatment of schizophrenia in the UK. A simulation model comparing olanzapine, risperidone and haloperidol. *Pharmacoeconomics*. 2000; 17(4): 383-9

American Psychiatric Association (APA). Treatment Recommendations for Patients with Major Depressive Disorder. Practice Guideline for the Treatment of Patients With Major Depressive Disorder, Second Edition. Arlington: American Psychiatric Publishing, Inc., 2000.

Anderson IM, Nutt DJ, Deakin JFW. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology (BAP) guidelines. *Journal of Psychopharmacology 2000*; 14(1): 3-20.

British National Formulary (BNF) 2003. London: British Medical Association and the Royal Pharmaceutical Society of Great Britain.

Broadhead WE, Blazer DG, George LK, Tse CK. Depression, disability days, and days lost from work in a prospective epidemiological survey. *JAMA 1990*; 264(19): 2524-2528.

DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: A Pathophysiologic Approach. Fifth edition. 2002; McGraw-Hill Companies, Inc. : New York, New York.

Kupfer DJ. Long-term treatment of depression. *Journal of Clinical Psychiatry* 1991; 52(Supplement 5): 28-34.

Medical Advisory Panel for the Pharmacy Benefits Management Strategic Health Group (PBMSHG), Department of Veterans Affairs. The pharmacologic management of major depression in the primary care setting. Veterans Health Administration Publication 00-0016, May 2000.

Melfi CA, Chawla AJ, Croghan TW, Hanna MP, Kennedy S, Sredl K. The Effects of Adherence to Antidepressant Treatment Guidelines on Relapse and Recurrence of Depression. *Arch Gen Psychiatry* 1998; 55: 1128-1132.

NHS Executive. Executive National Returns for 2002/2003. Leeds. Department of Health.

Palmer CS, Revicki DA, Halpern MT, Hatziandreu. The cost of suicide and suicide attempts in the United States. *Clinical Neuropharmacology* 1995; 18(suppl 3): S25-S33.

Personal Social Services Research Unit (PSSRU). 2003. Unit Costs of Health and Social Care. Canterbury: PSSRU.

Reimherr FW, Strong RE, Marchant BK, Hedges DW, Wender PH. Factors affecting return of symptoms 1 year after treatment in a 62-week controlled study of fluoxetine in major depression. *Journal of Clinical Psychiatry* 2001; 62(Supplement 22): 16-23.

Thomas CM, Morris S. Cost of depression among adults in England in 2000. *Br J Psychiatry*. 2003; 183 :514-9

Williams JWJ, Personal communication, May 21, 2003.

Williams JWJ, Mulrow CD, Chiquette E, Noel PH, Aguilar C, Cornell J. A systematic review of newer pharmacotherapies for depression in adults: Evidence Report Summary. *Annals of Internal Medicine* 2000; 132(9): 743-756.

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