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Clinical characteristics and unlicensed applications of licensed psychotropic drugs within a regional tertiary service for patients with affective disorders

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Abstract

Background: Referral to tertiary services is recommended when patients with mood and anxiety disorders have not responded to multiple treatments in primary or secondary care. Within specialist services, some patients undergo treatment with licensed psychotropic medications outside the narrow terms of their market authorization ('unlicensed applications'). We examined the demographic and clinical characteristics of patients referred to a regional specialist service to determine the extent of and factors associated with recommendations for unlicensed ('off label') prescriptions.

Methods: Retrospective examination of demographic and clinical characteristics and treatment recommendations in patients seen within a 5-year period. Patients were allocated to three broad diagnostic clusters (unipolar depressive disorders, bipolar disorder, anxiety disorders), and two groups (with or without comorbid disorders). We compared patients in whom all treatment recommendations were for licensed applications with patients in whom at least one treatment was for an unlicensed application, across a range of variables reflecting illness 'burden' (duration, inpatient treatment, electroconvulsive therapy, nonfatal self-harm, psychosis).

Results: From 177 new referrals, 148 patients (91 females, 57 males) could be placed within one of the three clusters. Many patients with bipolar disorder had not undergone treatment with lithium or formal psychological interventions in secondary care. Treatment recommendations involving unlicensed applications of medications were common (approximately 50%) in all clusters, but there were no significant differences in measures of illness burden between groups of patients, categorized according to licensed or unlicensed prescriptions.

Limitations: Retrospective examination of notes recorded for other purposes, within a single service, in which treatment recommendations might reflect idiosyncratic practice is a limitation of our findings. Also, examined variables could not provide a comprehensive indication of illness severity or functional impairment.

Conclusion: Our findings confirm that 'off label' prescribing is common in psychiatric practice. Treatment decisions relating to unlicensed applications appear to be influenced by factors other than overall illness burden.

Keywords: affective disorder services, licensed psychotropic medications, 'off label' prescribing, tertiary mood and anxiety disorder services, unlicensed psychotropic medications

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Introduction

Many patients with affective (mood and anxiety) disorders remain troubled by distressing depressive and anxiety symptoms even after a succession of evidence-based pharmacological and psychological treatments. In this situation, doctors may wonder whether they might prescribe a medication outside the narrow terms of its market authorization ('product licence') in an attempt to improve clinical outcomes. Many authorities agree that use of a drug outside the terms of its licence can be a necessary and beneficial part of clinical practice whereas others have raised concerns about patient safety and medical liability (see Baldwin *et al.*[1]). Prescribing a medicine within the terms of its authorization does not guarantee acceptability or effectiveness; neither does prescribing for an unlicensed medication necessarily reflect a lack of evidence for the treatment intervention.

Multiple factors can influence the decision to prescribe a medicine outside the terms of its licence (Royal College of Psychiatrists):[2]

(1) Previous licensed medications were ineffective or poorly tolerated.
(2) A medication may be effective and safe in another patient population but not approved for the treatment of a particular group of patients.
(3) A clinician may choose to avoid polypharmacy and prescribe just one medication in patients with two or more comorbid conditions.
(4) In the presence of a serious or life-threatening condition, a treatment that seems logical, though not approved, can be recommended.
(5) Cost-effectiveness considerations can sometimes lead to 'off label' prescribing.
(6) A pharmacist can dispense a medicine which has a lower maximum daily dosage than the dosage recommendations for a medicine obtained from another manufacturer and this can lead to inadvertent off-label prescribing.
(7) A patient may refuse to take an approved medication and so impel a clinician to prescribe 'off label'.

Tertiary services provide specialized health care for patients with complex and treatment-resistant conditions: patients are referred by secondary care services, although in rare circumstances, some are referred from primary care by general practitioners. Within the UK, National Institute for Health and Clinical Excellence (NICE)[3] guidance makes recommendations for referral to tertiary services for certain psychiatric disorders. For example, within the 'stepped care model' for organization of mental health services for people with obsessive–compulsive disorder or body dysmorphic disorder, steps 5 and 6 refer to services with specialist expertise able to offer inpatient care and intensive treatment. Similarly, the NICE stepped care model for generalized anxiety disorder (GAD)[4] suggests a role for highly specialist treatment (step 4), involving complex pharmacological or psychological interventions for patients with complex treatment-refractory conditions with marked functional impairment, or other risks such as self-neglect or self-harm.

It could be assumed that 'off label' prescriptions would be more common in patients with the most severe and treatment-resistant conditions, but factors associated with treatment decisions involving unapproved applications remain unclear. We therefore undertook a retrospective study within a single UK National Health Service regional specialist tertiary care service for patients with affective disorders, to examine relationships between clinical variables that reflect the overall burden of illness and prescribing patterns in patients within three broad illness clusters (unipolar depressive disorders, bipolar disorder, anxiety and related disorders).

Setting and methods

The service aims to improve clinical outcomes in patients with mood and anxiety disorders, particularly for those patients with persistent, complex and previously treatment-resistant conditions. Referrals of patients aged 18 years or older are accepted from regional consultant psychiatrists, but general practitioners can refer patients who are working as health professional in local services. Patients undergo comprehensive assessment of their psychiatric and other medical conditions: most patients are returned to secondary care mental health services with a series of sequenced treatment recommendations, but some patients are accepted into a time-limited treatment programme.

We examined the paper and electronic medical records of all patients referred to the service between January 2010 and December 2014, extracting details from referral letters and medical notes using a specifically designed data collection

instrument. Gathered data included dates of referral and assessment, age, sex and occupation of the patient, nature of the referring service, stipulated reasons for referral, current medical problems, diagnosis as stated in the referral letter, current psychological symptoms, previous psychiatric history, previously prescribed medications, presence of substance-use (including alcohol) problems, perceived risks, assessment diagnosis, and treatment recommendations (both approved and unapproved) and other patient management recommendations. Extracted data were transferred to Microsoft Excel (Microsoft, Redmond, Washington, USA) and IBM (International Business Machine Corporation, Armonk, New York, USA) SPSS Statistics 22 version was used to generate descriptive statistics. Patients were subsequently allocated to one of three broad diagnostic 'clusters' (unipolar depressive disorders, bipolar disorder, anxiety disorders) based on the observations recorded during a comprehensive clinical assessment. In each cluster, two subgroups were defined, based on the presence or absence of psychiatric comorbid conditions (depression and anxiety). We then examined licensed and unlicensed applications in each cluster and group and compared patients for whom all treatment recommendations were licensed with patients for whom at least one treatment was 'off label'. Recommendations for medication prescriptions were classified as 'off label' if they were not approved for that particular illness at the time of recommendation (e.g. quetiapine was authorized to treat bipolar depression in 2014), or not approved for that age group (e.g. many antidepressant medications are not approved in patients aged under 18 years) or prescribed above the approved dose for that age group (e.g. escitalopram at a dosage exceeding 20 mg per day)

We selected *a priori* a range of variables that reflect overall burden of illness [duration of mental health problems, history of a psychotic episode, history of nonfatal self-harm, history of admission to a psychiatric unit, history of electroconvulsive therapy (ECT)] and examined the potential influence of these variables on treatment decisions. We then compared the group of patients in whom treatment recommendations included at least one unlicensed application with the group of patients in whom all recommendations were within the terms of their product licences, across the specified markers of illness burden (analysis based on Pearson chi-square and Fisher's exact test comparisons).

Data were gathered from routine medical records compiled for other purposes, within the context of an approved clinical audit (Southern Health NHS Foundation Trust), for which NHS ethics committee approval and informed consent are not required. All data were anonymized in the data collection instrument.

Results

Referral, demographic and clinical characteristics (Table 1)

The referred group comprised 177 patients (102 women, 75 men), 148 of whom (91 women, 57 men) could be placed within the principal clusters of unipolar depressive disorders (n = 65), bipolar disorder (n = 54) or anxiety and related disorders (n = 29): 32 patients had current comorbid anxiety and depressive disorders. Twenty-nine patients had a primary psychiatric diagnosis other than an affective disorder (e.g. schizophrenia or alcohol dependence) and their data were excluded from further analysis. There were few differences between the three main clusters in sex distribution or mean age, but patients with unipolar disorders were more likely to be employed than patients with anxiety disorders. In all three clusters, the most common primary reason for referral was nonresponse to previous treatment (unipolar disorders 72.3%, bipolar disorder 79.6%, anxiety disorders 82.7%), this reason being especially common (93.8%) in patients with current comorbidity.

The most common stipulated secondary reason for referral was for recommendations on further treatment options (unipolar disorders 90.7%, bipolar disorder 92.6%, anxiety disorders 96.5%).

Current psychological syndromes, medical history and previous treatments (Table 2)

A current depressive syndrome was the most common current symptom complex in unipolar and bipolar disorder clusters. Only one patient in the bipolar group presented with current elated mood. In the bipolar disorder cluster, 15 patients (27.7%) had unstable or rapidly cycling mood. Few patients had current psychotic symptoms alongside depression (6% of unipolar patients, 7.4% of bipolar patients). Psychiatric comorbidity was common in all clusters, being most frequent (41.4%) in patients with an anxiety disorder: all three clusters had notable rates of

Table 1. Basic demographic data for total group.

	Unipolar depressive disorders* (*n* = 65)	Bipolar disorder (*n* = 54)	Anxiety disorder (*n* = 29)	Total (*n* = 148)
Sex				
Male, *n* (%)	24 (36.9)	23 (42.5)	10 (34.4)	57 (38.5)
Female, *n* (%)	41 (63.07)	31 (57.4)	19 (65.5)	91 (61.4)
Age				
Mean (years)	52.4	50.7	48.7	50.8
Age range (years)	20–84	18–80	23–72	18–84
Occupation: all				
Employed, *n* (%)	28 (43)	21 (38.8)	8 (27.6)	57 (38.5)
Unemployed, *n* (%)	22 (33.84)	15 (27.7)	10 (34.4)	47 (31.7)
Not stated, *n* (%)	15 (23)	18 (33.3)	11 (37.9)	44 (29.7)
Health professionals				
Employed, *n* (%)	13 (20)	7 (12.9)	3 (10.3)	23 (15.5)
Unemployed, *n* (%)	3 (4.6)	3 (5.5)	0 (1)	6 (4)

*Includes primary diagnoses of depressive episode, recurrent unipolar depressive disorder and dysthymia.

current endocrine (3.0–17.2%) and cardiovascular (12.0–14.0%) disease. The majority of patients had a recurring condition (unipolar disorder 92.3%, bipolar disorder 92.6%, anxiety disorder 86.2%), this being most common in the currently comorbid group (96.8%). A history of inpatient psychiatric care was common (unipolar disorder 38.4%, bipolar disorder 46.2%); the proportion who had undergone ECT was higher in unipolar patients (29.4%) than in bipolar patients (20.4%); and only 13% of bipolar patients had undertaken formal psychological interventions.

Previous psychotropic drug treatment

Taken as a group, selective serotonin reuptake inhibitors (SSRIs) were the most common prior prescriptions in all three clusters, though less common in bipolar patients: serotonin–noradrenaline reuptake inhibitors (SNRI) had been as frequently prescribed as SSRI in unipolar patients, but less frequently in other clusters. Prior prescriptions of tricyclic antidepressants (TCAs) were less common than prescriptions for SSRI or SNRI in all three clusters; mirtazapine prescriptions were less frequent in patients with bipolar disorder or anxiety disorders than in patients with unipolar depressive disorders; and prescriptions for monoamine oxidase inhibitors (MAOIs) were uncommon in all three clusters. Pregabalin prescriptions were more common in patient with anxiety disorders. In patients with bipolar disorder, 74% had previously undergone treatment with lithium. A substantial proportion of patients had undergone prior treatment with an antipsychotic drug in all three clusters.

Recommendations for further treatment

In the unipolar cluster, the most frequent recommendation was for switching outside the current antidepressant class. In the bipolar cluster, the most frequent recommendations were for adjustment of current anticonvulsant dosage (44.4%) or introduction of an anticonvulsant (42.5%). In the anxiety disorder cluster, the most frequent recommendations were for adjustment of antidepressant dosage (62.1%) or the introduction of an antidepressant (44.8%).

Patients with or without current comorbidity did not differ significantly across the range of variables selected to reflect overall illness burden.

Table 2. Sources, reasons for referral to service, psychiatric and physical comorbidities.

	Unipolar depressive disorders*	Bipolar disorder	Anxiety disorder	Comorbid depression and anxiety disorder
Number of patients	65	54	29	32
Referrer				
Psychiatrist : GP : missing	60 : 3 : 2	51 : 1 : 2	23 : 4 : 2	30 : 1 : 1
Local NHS trust, *n* (%)	38 (58.5)	39 (72.2)	15 (51.7)	17 (53.1)
Other NHS trusts, *n* (%)	27 (41.5)	15 (27.7)	14 (48.3)	15 (46.8)
Psychiatric comorbidity, *n* (%)	11 (17)	12 (22.2)	12 (41.4)	3 (9.3)
Physical comorbidity, *n* (%)				
CVS	8 (12.3)	8 (14.8)	4 (13.7)	4 (12.5)
Respiratory	3 (4.6)	3 (5.5)	0 (–)	0 (–)
Musculoskeletal	6 (9.2)	5 (9.2)	3 (10.3)	3 (9.3)
Endocrinal	10 (15.4)	9 (16.6)	5 (17.2)	1 (3)
Neurological	8 (12.3)	8 (12.3)	2 (6.9)	0 (–)
Others	9 (13.8)	10 (18.5)	4 (13.7)	7 (21.8)
Current symptom clusters, *n* (%)*				
Depression	57 (87.7)	28 (51.8)	16 (55)	21 (65.6)
Anxiety	25 (38.4)	13 (24)	25 (86.2)	24 (75)
Elated mood	0 (–)	1 (1.8)	0 (–)	0 (–)
Unstable mood/rapid cycling	0 (–)	15 (27.7)	1 (3.4)	0 (–)
Psychotic symptoms	0 (–)	0 (–)	0 (–)	0 (–)
Elation and psychosis	0 (–)	0 (–)	0 (–)	0 (–)
Depression and psychosis	4 (6)	4 (7.4)	0 (–)	1 (3.1)
No current psychotic symptoms	4 (6)	3 (5.5)	0 (–)	1 (3.1)

*Includes primary diagnoses of depressive episode, recurrent unipolar depressive disorder and dysthymia.

Unlicensed applications of licensed drugs

Recommendations for unlicensed applications were common in all three clusters (bipolar disorder 48.1%, unipolar disorders 50.8%, and anxiety disorders 51.7%). In the unipolar group, there were similar proportions of patients for whom only licensed treatments and for whom at least one unlicensed application was recommended (33 and 32 patients, respectively). *Post hoc* analysis found no significant influences of sex on the likelihood of unlicensed prescribing. Across all three clusters, a total of 74 patients were recommended unlicensed treatments, among whom, 46 (62.1%) were females. In the unipolar depressive disorder cluster, unlicensed prescriptions were recommended in 50% of males and 51.2% of females ($p = 0.924$), in the bipolar disorder cluster unlicensed prescriptions were recommended in 52% of males and 45% of females ($p = 0.610$),and in the anxiety disorder cluster, unlicensed prescriptions were

recommended in 40% of males and 58% of females ($p = 0.359$). By contrast, there was a significant influence of age: unlicensed prescriptions were recommended in 53% of patients aged under 65 years (combining all three clusters), compared with 28% in patients aged 65 years or older ($p = 0.023$).

Using history of treatment with ECT as a marker of illness severity, 30.3% of patients in the 'off label' group and 28.1% of the exclusively licensed group had received ECT ($p = 0.847$). In the 'off label' group only 30.3% of patients had undergone inpatient psychiatric treatment, as compared with 50% among the exclusively licensed group, but this difference was not significant ($p = 0.105$). By contrast, only 3.0% of patients in the 'off label' group compared with 18.1% in the exclusively licensed group had a history of psychosis, this difference being marginally significant ($p = 0.048$). In the bipolar group, large proportions of patients with long-term illness were found in both the 'off label' and exclusively licensed groups (93.9% and 87.5%, respectively: $p = 0.321$). Only 12.1% of patients in the 'off label' group and 15.6% in the exclusively licensed group had a history of self-harm, there being no difference between groups ($p = 0.48$).

In the anxiety disorder group, there were similar proportions of patients (15 and 14 patients, respectively) who were recommended to receive 'off label' or exclusively licensed prescriptions. As anticipated, few patients had undergone treatment with ECT (one patient in the off-label group, no patient in the licensed group). Only one patient in either group had undergone previous inpatient psychiatric treatment; and only one patient from each group had a history of psychosis. Large proportions of patients in both groups (93.3% 'off label', 78.6% exclusively licensed) had a history of long-term illness ($p = 0.272$). Only one patient (in the 'off label' group) had a history of self-harm.

A total of 101of 148 patients had some form of physical comorbidity, and 56% of these patients received a recommendation for an unlicensed medication. The proportion of patients with physical comorbidity who received a recommendation for an unlicensed application did not vary greatly across the three clusters (unipolar depressive disorder 41.8%, bipolar disorder 35%, anxiety disorder 55.5%).

Discussion

The limitations of this study include its small sample size, retrospective nature, use of clinical diagnoses rather than a structured interview based on the International Classification of Diseases, 10th edition, or Diagnostic and Statistical Manual of Mental Disorders criteria, reliance on medical notes recorded for other purposes for much of the information regarding the history of patients, and basis within a single specialist tertiary care service. We did not collect data prospectively to allow an exploration of the influence of variables like sex, age and physical comorbidity on the decision of off-label prescriptions (but include data based on *post hoc* exploratory analyses). The principal finding is that treatment recommendations involving an 'off label' application were common across three broad diagnosis-related clusters (unipolar depressive disorders, bipolar disorder, anxiety and related disorders).

These findings align with those from other studies: for example, an audit of antipsychotic drug prescribing over 5 years in a secondary care NHS trust found that approximately 40% of prescriptions were 'off label';[5] a cross-sectional survey of prescriptions for mood-stabilizing drugs in 249 patients in another tertiary care unit found that 28.5% were receiving prescriptions for unapproved indications;[6] and the proportion of prescribing for unlicensed applications was found to be higher (66%) in a retrospective evaluation within an intellectual disability clinical service.[7] The current findings are perhaps not surprising, given the nature of the clinical population, namely patients with long-standing complex and typically treatment-resistant affective disorders.

There were no significant differences between groups ('off label' *versus* exclusively licensed) on preselected variables reflecting overall burden of illness, which suggests that recommendation for an unapproved application in this group of treatment-resistant patients are influenced by other factors. Randomized clinical trials are mostly designed to assess the short-term efficacy and safety of a novel drug under optimal clinical situations when compared with a nonspecific control treatment (placebo) in order to fulfil regulatory standards for drug authorization and marketing.[8] Recruitment criteria for such trials are restrictive (typically involving a single diagnosis, absence of comorbidity and concomitant mediation, and readiness to many detailed follow-up appointments, etc.) and the findings from trials, and the

ensuing licences arising from those trials, may not be generalizable to more routine clinical practice.[9] It has been argued that licensing of medicines should relate rather better to real-world patients and more routine clinical use.[10] A more systematic and coordinated, approach is required to both recognize and develop the evidence base for pharmacotherapy in psychiatry, which would benefit both patients and prescribers.[9]

This is one of very few studies describing a tertiary referral service for patients with treatment-resistant mood and anxiety disorders. Data from this study provide some information on current management options for patients with treatment-resistant affective disorders.

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Conflict of interest statement

Professor Baldwin was the Chair of a working group of the Royal College of Psychiatrists, charged with producing guidance on unlicensed applications of licensed drugs in psychiatric practice (College Report CR210).

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