Off-licence prescribing and regulation in psychiatry: current challenges require a new model of governance

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Abstract: The growing worldwide use of pharmaceuticals is managed in some countries by a regulatory system which sharply divides legal use into licensed and unlicensed categories. We examine how for the range of psychotropics this simultaneously restricts the possible benefits to patients, prescribers and producers in some domains, while failing to manage the risks in others. A more flexible system, which shares at an earlier stage experience and evidence on benefits and risks in patients, previously marginalized on the grounds of age, diagnosis or comorbidity, would aid the development of safer, more effective 'real-world prescribing'. Practical recommendations are made for a new model of research and prescribing governance, to enable more effective repurposing of these treatments.

Keywords: antidepressants, antipsychotics, off-label prescription, off-licence, mental health, pharmacotherapy, psychotropic medication, repurposing

Introduction

The prescription of psychotropic medicines across all age groups is rising worldwide [Wong *et al.* 2004; Exeter *et al.* 2009; Deambrosis *et al.* 2010; Verdoux *et al.* 2010; Ilyas and Moncrieff, 2012], comprising a US$330 billion market [Murashev, 2012], more than a third of global pharmaceutical sales. In the US antidepressants comprise the largest category of prescribed drug ranked by expenditure, and their use continues to increase by around 20% each year. The prescription of antipsychotic medicines, 13th by expenditure, is increasing even more rapidly [Zuvekas, 2005]. In England, the estimated health, social and informal care cost for mental illness was £22.5 billion per annum in 2007 [McCrone, 2008]. Within this, psychotropic medication is a significant area of growth, as antidepressant prescriptions have increased by 10% and antipsychotics by 5% year on year [Ilyas and Moncrieff, 2012]. In 2010 they accounted for almost 9% of all prescriptions.

Multiple factors have contributed to these trends. Medical practice is changing; in psychiatry, new and more expensive antidepressants and antipsychotics have superseded old ones and, crucially, more people are being treated and prescribed for [Zuvekas, 2005]. Public health demographics are changing; the number of people with chronic conditions is rising [Busse *et al.* 2010] and as life expectancy improves the 'at risk pool' for many disorders increases [Winker and Deangelis, 2010]. Pharmaceutical advertising is becoming increasingly targeted, not only at the prescriber, but also at the patient or consumer [Donohue *et al.* 2007].

The licensing process

One of the key controls of medicines use is the licensing process, with prescribing practices beyond this known as off-licence or 'off-label'. In the UK a drug's marketing authorization specifies its licensed dose range, form and target disorders, a role performed by the Medicines and Healthcare products Regulatory Agency (MHRA) and the Food and Drug Administration (FDA) in the US. These agencies are primarily concerned with defining the market entry requirements of medicines rather than policing future prescribing practices.

In the UK the MHRA process for licensing medicines before they come to market is governed by UK and European Union law. The MHRA assess

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the quality, safety and efficacy data submitted to it from human clinical trials determined, designed and conducted by the pharmaceutical companies. Such trials are conducted in a hierarchical sequence of studies that first establish safety in healthy volunteers (phase I) and then in highly selected patients, to establish proof of concept, dose and side-effects (phase II). Phase III trials are typically randomized, double blinded and test clinical efficacy, while phase IV trials are usually conducted after licensing and establish longer-term risks and effectiveness. Clinical trials in psychiatry are almost always restricted to studies of 'compliant' working age adults, usually with a single disorder that meet strict diagnostic criteria according to the International Classification of Diseases (ICD) or the Diagnostic Statistical Manual of Mental Disorders (DSM) schemes. The patients typically lack comorbidity [Healy and Nutt, 1998] and have capacity to give informed consent [Welie and Berghmans, 2006]. MHRA authorization, provided on the basis of such trials, is then only granted to patients whose characteristics match the inclusion criteria of the original trial subjects. Therefore, for example older age adults, children and pregnant women, as well as vulnerable adults with complex (physical and mental) health comorbidities are almost universally excluded from marketing authorisations and by default will rely on off-licence prescription for treatment [Baldwin and Kosky, 2007]. Similar restrictions apply to the determination of dosing regimens. The generalizability of such trials to more typical clinical populations, with comorbidity or who lack capacity is rarely addressed.

Clinicians are in fact free to prescribe outside the licensing terms ('off-licence') with certain caveats clearly outlined in the General Medical Council's Good Practice guidelines for Doctors [General Medical Council, 2008], but in doing so, they must understand that they operate outside the approved licence and simultaneously assume greater professional responsibility and liability. These guidelines recommend that the off-licence prescriber is satisfied that sufficient evidence exists, or that they have sufficient experience of using the medicine to believe it will be safe and effective. The prescriber should be aware of the requirements and make a clear record of the reasons for prescribing off-licence in the medical notes.

The National Institute for Clinical Excellence (NICE) sets out further guidance on the use of drug treatments for mental disorders which health professionals are expected to take into account when prescribing. There are examples where NICE recommends off-licence use of psychotropics. For instance in the 2005 post-traumatic stress disorder (PTSD) guidance, where drug treatment with paroxetine, mirtazapine, amitriptyline or phenelzine, under appropriate supervision was recommended for those patients who expressed a preference not to engage in trauma-focused psychological work [National Collaborating Centre for Mental Health, 2005]. At the time paroxetine was the only one of those recommended with a UK product licence for PTSD. Occasionally NICE withholds approval for some psychotropics on the grounds of costs. For example, the 2005 revised NICE dementia guidelines confirmed that the cholinesterase inhibitors donepezil, rivastigmine and galantamine are effective and safe in treatment of Alzheimer's disease but concluded that on current evidence these drugs are not cost effective and should not be prescribed by the NHS [Overshott and Burns, 2005].

The extent of off-licence prescribing in psychiatry

Off-licence prescribing of psychotropic medicines can be found in every major branch of psychiatry, working age adult, older adult, child and adolescent, intellectual disability, and forensic, also in subspecialities such as perinatal psychiatry [Baldwin and Kosky, 2007; Haw and Stubbs, 2007a; Leslie *et al.* 2009]. In 2000, 65% of National Health Service (NHS) doctors reported that they had prescribed 'off-label' within the last month [Lowe-Ponsford and Baldwin, 2000]: 12% for a patient outside the specified population, for example the elderly; 19% had exceeded the indicated dose range; and 49% for a different indication to that licensed [Lowe-Ponsford and Baldwin, 2000]. In the in-patient setting one survey found that, 7% of all prescriptions were made for unlicensed indications or at doses that exceeded the approved maxima [Douglas-Hall *et al.* 2001]. Similar practices are found in Germany, where almost half (47%) of all psychotropic prescriptions in 2003/4 were deemed 'clearly' or 'probably' off-label [Assion and Jungck, 2007]. In the US almost 90% of all DSM-IV disorders have no FDA-approved drug for their treatment [Devulapalli and Nasrallah, 2009], although more have licensed medicines for specific symptom clusters [Pascual *et al.* 2010]. Furthermore, some prescribing is considered 'near label', where a medicine is used for an unlicensed indication, but where the disorder is similar in nature or symptomology to that

licensed. For example, the use of antidepressants as a maintenance and prophylactic treatment in a patient with recurrent depression. Thus, it is sometimes helpful to consider prescribing behaviour in terms of a spectrum of increasingly unlicensed applications [Baldwin and Kosky, 2007].

Antipsychotics

Globally off-label uses account for up to 65% of all antipsychotic prescriptions [Weiss *et al.* 2000; Barbui *et al.* 2004; Hodgson and Belgamwar, 2006; Leslie *et al.* 2009] with common off-licence uses including depressive and bipolar affective disorders, dementia, especially when complicated by challenging or aggressive behaviour, anxiety disorders, alcohol and drug dependence, personality disorder, post-traumatic stress and pervasive developmental disorders [Leslie *et al.* 2009]. Quetiapine is the most frequently prescribed off-label antipsychotic in the US, followed by risperidone and then first-generation medicines [Leslie *et al.* 2009]. In one modest UK study olanzapine was the most commonly prescribed, and was given for a disorder other than schizophrenia in 134 out of 310 prescriptions [Hodgson and Belgamwar, 2006]. With an increase in better quality randomized controlled trial (RCT) data, the licensing indications for olanzapine have since broadened and now include mania and prophylaxis in bipolar disorder and for the treatment of agitation in schizophrenia and mania. Nevertheless frequent off-licence indications include PTSD, obsessive–compulsive disorder, borderline personality disorder and dementia [Maglione *et al.* 2011].

In addition to prescriptions that are clearly for unlicensed indications, antipsychotics prescribed on an 'as required' in addition to regular basis often contribute to cumulative daily dose totals that exceed the licensed maxima [Milton *et al.* 1998], with olanzapine the most commonly prescribed antipsychotic above its licensed dose [Douglas-Hall *et al.* 2001; Hodgson and Belgamwar, 2006]. This practice in conjunction with polypharmacy is a major contributor to high-dose prescribing. One in five of a UK adult psychiatric inpatient sample were prescribed antipsychotics that exceeded British National Formulary (BNF) daily dose limits, with polypharmacy involved in the majority [Lelliott *et al.* 2002]. The data on the benefits of such an approach at best is unconvincing at present, with support largely limited to case reports and open-label trials [Stahl and Grady, 2004], while there is evidence of a significant increase in adverse effects [Taylor *et al.* 2002].

The lack of evidence supporting antipsychotic prescribing is starkest among the groups rarely recruited into clinical trials, including children, older adults and the intellectually disabled. Yet prescribing to these groups continues. To illustrate Doey and colleagues found that over 90% of child psychiatrists and developmental paediatricians prescribed second generation antipsychotics, with 12% of these prescriptions to children less than 9 years of age [Doey *et al.* 2007]. Our increasing awareness of the long-term metabolic consequences of these second-generation agents in this group is only now accumulating through clinical experience [Sikich *et al.* 2008]. At the other age extreme, The National Nursing Home Survey (NNHS) [Kamble *et al.* 2010] found the same widespread use in the elderly, with six out of seven second-generation antipsychotic prescriptions in that group off-label. In in-patient services that support those with an intellectual disability and challenging or aggressive behaviour, the majority were prescribed an antipsychotic [Deb and Fraser, 1994; Marshall, 2004; Sawhney *et al.* 2006], although with no RCT data to guide practice [Brylewski and Duggan, 2004].

Anticonvulsants and mood stabilizers

Off-label use of anticonvulsants in psychiatry is increasing. Carbamazepine and sodium valproate licensed primarily for seizure control in epilepsy are the most frequently prescribed mood stabilizers for nonlicensed indications [Taylor *et al.* 2000] that include particularly mood control in mania and schizoaffective disorder [Bradford *et al.* 2003; Nasrallah *et al.* 2010] and to augment clozapine in treatment-resistant schizophrenia [Haw and Stubbs, 2005]. Sodium valproate is now increasingly prescribed as an anti-aggressive agent across a variety of mental health disorders, with inconsistent RCT data to support this practice. Valproate has reduced impulsive aggression in some studies [Hollander *et al.* 2003; Stanford *et al.* 2005], but not others [Hellings *et al.* 2005]. In practice up to a third of inpatients in forensic psychiatric settings are prescribed a mood stabilizer, of which almost all are off-licence [Haw and Stubbs, 2005].

Antidepressants

In 2011, just fewer than 46.7 million prescriptions for antidepressants were dispensed in

England [The Health and Social Care Information Centre (HSIC), 2011]. They are often prescribed off-licence and in the absence of an established evidence base [Royal College of Psychiatrists, 2007]. For example, about 40% of all antidepressant prescriptions are for nonmood disorders [Ornstein *et al.* 2000], with the newer medicines increasingly seen as practical and acceptable treatments for illnesses ranging from the depressive symptoms of bipolar disorder, to anxiety and eating disorders [Carter *et al.* 2003; Appolinario and McElroy, 2004]. The first of these continues despite evidence linking antidepressants to an increased risk of mania, and a worse long-term prognosis [Ghaemi *et al.* 2003; Matza *et al.* 2005].

Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed medicines in child and adolescent services [Lee *et al.* 2012], but with less than 1 in 10 prescriptions in the US linked to an FDA-endorsed indication. SSRI prescriptions to children declined significantly after the Committee on Safety of Medicines (CSM) report linked their use to an increased risk of suicidal behaviour, but since 2005 prescription rates have gradually risen again [Wijlaars *et al.* 2012].

Anxiolytics and hypnotics

Benzodiazepines are widely prescribed, well beyond their original indications as anxiolytics and hypnotics, for example in schizophrenia [Taylor *et al.* 2002], panic disorder [Chouinard, 2006], and depression [Valenstein *et al.* 2004]. UK data shows their extensive use in both acute and long-term mental health settings [Summers and Brown, 1998; Paton *et al.* 2000], where they are commonly prescribed in preference to other psychotropics [Davies *et al.* 2007]. Diazepam and lorazepam are the most commonly prescribed in long stay wards [Haw and Stubbs, 2007b], typically for anxiety, aggression and agitation. In practice more than 90% of benzodiazepine prescriptions in that setting were off-label, predominantly because the duration of treatment exceeded the time-limited marketing authorization (over 80%), the indication (almost 50%), or both. Although there is a school of thought that benzodiazepines offer a safety advantage, this may not in fact be the case. Recent findings have linked benzodiazepines with a significant increase for instance in mortality among patients with schizophrenia compared to both antidepressants and concomitant antipsychotics [Tiihonen *et al.* 2009, 2012].

Restrictions of the current licensing process

The rise in off-licence prescribing is in part a product of the stringent regulatory frameworks that govern drug licensing, but authorities clearly face major practical challenges. Most regulators agree that a necessary element of day-to-day psychiatric practice is the prescription of psychotropics beyond the specifications of their licensed indications [Healy and Nutt, 1998; Baldwin and Kosky, 2007] and that patients should receive the most up-to-date and beneficial medicines for their illness [Nutt and Goodwin, 2011]. In fact, however, prescribing off-licence does not equate to evidence-free prescribing and authorities have an obligation to confirm the effectiveness (efficacy and safety) and best use of medicines in real clinical practice before granting authorisation or in a process of review[Nutt and Goodwin, 2011]. For example, the NICE Guidelines for the treatment of borderline personality disorder stated that medication should not be used specifically for BPD or its individual symptoms [National Collaborating Centre for Mental Health, 2009], but has not yet responded to a challenge from a Cochrane systematic review that followed shortly afterwards that reached different conclusions [Lieb *et al.* 2010].

For psychotropic medications at least, the requirement for monotherapy in multiple randomized placebo-controlled trials may be impractical. Over the last 10 years just one novel antidepressant, aglomelatine was approved in Europe, compared with 10 new antiepileptics [Wise, 2011]. Some have argued that excessive regulations are proving too obstructive to conduct research efficiently [Nutt and Goodwin, 2011] and that the regulatory process has sprawled into a minefield, costly in both time and money [Baldwin and Kosky, 2007]. Pharmaceutical companies are driven by practical and economic considerations [Stafford, 2008]; rather than a prioritization of drug research based on public health needs [Segman and Weizman, 2008]. One cost of this may be the withdrawal over the past year of a number of major pharmaceutical companies including GlaxoSmithKline and AstraZeneca from the mental health field, citing a lack of economic viability [Wise, 2011]. If clinicians are prepared to prescribe off-licence, there is less incentive to establish that licence in the first place. It is also possible, however, that whilst our pharmacological understanding of the major mental illnesses is developing, in fact the pharmacological targets of

our medicines has evolved less dramatically. While some relatively novel pharmacological targets have emerged, it still remains true that all effective antipsychotics still have some dopamine antagonism properties, and antidepressants similarly all act on monoamine systems.

Once in the market, further regulations apply. Advertising strategies are carefully supervised in the licensing framework. The endorsement of an off-licence indication for a medicine can lead to harsh penalties. Pfizer was recently fined US$2.3 billion for off-licence marketing of four of its medicines including the antipsychotic agent ziprasidone (Geodon) [Ratner, 2009]. Some have argued that restrictions on advertising are in effect a restriction of commercial free expression, and that the regulatory systems should be sufficiently flexible to recognize 'real-world' prescribing practices [Stafford, 2008], which are often driven by patient need and expectation. Of course if such real-world practices are not supported by any real evidence then they should be challenged.

A major incentive for novel drug investigation is the opportunity to secure a patent, granting the holder a 20-year sales monopoly [French, 2005]. However, once the patent has expired, pharmaceutical companies have little or no further incentive to establish new indications, given competition from low-cost generic suppliers, so any such work beyond that time will almost inevitably fall to independent academics [Devulapalli and Nasrallah, 2009].

The availability and licensed indications for drugs differs between countries and is often based on marketing decisions, as well as but also different national regulation requirements. For example the atypical antipsychotic ziprasidone, was approved in a variety of countries including the USA in 2001[Nemeroff *et al.* 2005]. It is indicated for schizophrenia, as monotherapy or adjunctive therapy for acute mania, and maintenance therapy for mania and bipolar disorder. But more than 10% of patients prescribed the drug have developed modest QTc interval prolongation, and so the launch of the atypical antipsychotic ziprasidone continues to be delayed in the UK in part due to the request for mandatory cardiovascular monitoring that may have limited sales and influenced requirement in other jurisdictions [Abdelmawla and Mitchell, 2006].

Prescriber practices, safeguards and checks

Off-licence prescribing can involve the purposeful prescription of a medicine, outside its licensed target group or dose, but justified on the basis of the best available evidence and discussed collaboratively with a consenting patient; or it may be unintentional, used by a physician who is unaware that the licensed parameters have been breached [Uzoechina *et al.* 2011] or that the evidence is scant or nonexistant. In fact prescribers who are aware of the off-label status of a product often overestimate the strength and quality of the evidence to support their practice, and rely on personal experience as justification. A study of psychotropic prescribing in two large UK medium secure units found less than 30% of all off-label prescriptions were supported by meta-analyses or well-designed RCTs, while lesser quality experimental evidence supported about 30%, expert opinion about 40%, while 5% was unsupported by any evidence [Haw and Stubbs, 2010]. Others have reported that the majority of off-label prescribing for children and adolescents had either inconclusive or no evidence at all supporting efficacy [Czaja and Valuck, 2012].

The reality is that physicians are often unaware of the indicated disorders for many medicines. In one large US study of primary care physicians and psychiatrists, less than 50% could identify the FDA approved diagnoses for selected medicines [Chen *et al.* 2009]. Similar rates are seen in the UK. General practitioners (GPs) are unaware of the extent of off- label prescribing [Ekins Daukes *et al.* 2005], although many are aware of the explicit problems with dosing in children [Ekins Daukes *et al.* 2005]. Perhaps most importantly clinicians often have only a limited understanding of the issues around off-label prescribing, the frequency of side effects and lack of efficacy data. There can also be problems concerning informed consent [Ekins Daukes *et al.* 2005], as while prescribers of psychotropics may be aware that the prescription is off-label, it is clear that it is only rarely known by the patient [Haw and Stubbs, 2005].

Overall there are few established systems to support and manage off-licence medicine prescribing [Ansani *et al.* 2006]. Psychiatrists continue to express unease about the extent of prescribing off-licence in the mental health field and the legal, as well as clinical risk that they expose themselves to [Lowe-Ponsford and Baldwin, 2000]. Furthermore,

while it is not considered a breach of care to prescribe off-licence, if and when that decision is supported by clinical evidence and a broad body of clinical opinion, it is possible to face sanction if a off-label treatment is withheld [Henry, 1999]. In reality, only a small minority are ever involved in such a grievance [Lowe-Ponsford and Baldwin, 2000].

Safeguards can be implemented to ensure drug accessibility is controlled, and that prescribing remains the prerogative of appropriately trained clinical practitioners. Medicines prescriber information sheets list patient safety data, while black-box warnings continue to update clinicians when extra vigilance is needed [Stafford, 2008]. In the UK at least there appears to be a confusing range of opinion on what can be prescribed and for whom, from national medicines information services, expert opinion such as the Maudsley Prescribing Guidelines [Taylor *et al.* 2012], the MHRA and NICE, to guidance from individual hospitals, NHS trusts and insurance companies [Bücheler *et al.* 2002].

A framework to protect unlicensed groups

Blinded randomised controlled trials remain the highest quality individual study design. They provide the most reliable and objective data to support effectiveness, efficacy and safety of innovative treatments, and need to be conducted before regulators award full licensed approval for a medicine. However, change in the current regulatory process is required, to generate greater incentive to conduct new drug research for mental disorders and, to guarantee long-term added efficacy and safety [Segman and Weizman, 2008].

The 2011 European College of Neuropharmacology (ECNP) summit report [Nutt and Goodwin, 2011] made a number of proposals aimed at incentivising those working on novel compounds for brain disorders to gain a licence and launch to market. These include lengthening the patent time for new drugs, examining alternative methods of investigating application to novel indications, removing the requirement for a 6-month, placebo-controlled trial before licence approval (moving Europe into line with the US), and revising the regulatory route by examining alternative methods of investigating application to novel indications leading to provisional approval. Smaller RCTs, cohort and case-control studies could also play a role in contributing to the information that underpins the licensing evidence base [Harbour and Miller, 2001].

Others have suggested that new drug development should in part be driven along the lines of strategic long-term health needs. Recommendations might include allotting public funding for drug trials based on the clinical need to establish evidence based data [Segman and Weizman, 2008], or awarding provisional approval that could be withdrawn if satisfactory clinical data did not later validate clinical benefits or long-term safety [Wood, 2006].

While the motives for the growing practice of 'repurposing' are often strategic and financial [Oprea and Mestres, 2012], considering complementary trials for potential secondary indications and excluded groups, earlier on in the medicines licensing process should also become more common place [Stafford, 2008].

There is a need for strong drug regulation. The MHRA and other regulatory authorities have their origins in the medicines disasters of the early 1960s and the establishment of the Committee on Safety of Drugs (CSD) in 1964. These systems are essential to protect patients, but it can be argued that in an effort to do so they have become overly restrictive and the licensing system is now inhibiting positive clinical developments.

At present clinical trials are commonly designed to show the short-term efficacy and safety of a novel drug under optimal clinical situations in contrast with no treatment (placebo), to fulfil regulatory standards for drug authorization and marketing [Segman and Weizman, 2008]. Participants are usually recruited using highly restrictive criteria including only a single diagnosis, no comorbidity or substance misuse, and being able to reliably attend long-term follow up. Such features are not generalizable to routine clinical practice. Medicine licensing needs to relate better to real-world patients and clinical use [Chen *et al.* 2009].

A more pragmatic approach could be to include patients with multiple diagnoses and other heterogeneity. Establishing an accessible evidence base that associates a drug with a specific but off-label indication has already been recommended for children [Tishler and Reiss, 2011]. Such a system would collect and collate results across a variety of trial designs developing an accessible and

transparent open clinical trial registry or repository [Ernest *et al.* 2007; Tishler and Reiss, 2011]. Furthermore while clinicians continue to prescribe medicines in novel and off-licence situations during routine practice, this represents an opportunity to collect efficacy and safety data [Baldwin and Kosky, 2007]; it is vital these applications are recorded and reported. Others authors [Tishler and Reiss, 2011] have recommended the systematic collection of data on adverse effects. Studying how uncorroborated off-label use disseminates into treatment practice may help judge the standards of existing regulatory policies, and would contribute to a credible body of data to guide prescribers in common situations and the pharmaceutical industry on which drugs and when are strong candidates for further investigation.

These proposals challenge clinicians to remain informed of the evidence base as it develops [Stafford, 2008]. As healthcare makes the transition to electronic health records, increasingly precise documentation of diagnosis, prescribing and outcomes is likely to be achievable [Walton *et al.* 2008]. Other solutions include carefully accumulating and analysing post marketing information and focusing on efficacy and safety data beyond the official licence, in the style of Cochrane reviews and the Maudsley Prescribing Guidelines [Stafford, 2008]. There is also a clear need for more resources to be devoted to making the evidence base as accessible as possible for practitioners, such as the development of a concise yet comprehensive guide which will be frequently updated and can cite the level of evidence supporting common off-label use [Walton *et al.* 2008]. This goes beyond what current classification frameworks are able to offer to date.

A funded national specialist mental health centre, dedicated to off-label prescribing and research, would provide a recognized source of information for practitioners and lead to major improvements in appropriate psychotropic prescribing. It could also be the base for systematic reviews to gather and evaluate previous RCT support for psychotropics and recognize where the largest information gaps exist.

Recommendations

Society, through its governing institutions, has a duty to balance the expectations of the various stakeholders involved in providing evidence-based healthcare. These include the regulatory authorities, ethics committees, prescribers, pharmaceutical companies, academia, public and private healthcare providers and most importantly the people who receive treatment. As we have shown for psychotropics, the current system offers a superficially clear, but highly restrictive, licensing system, while tacitly accepting that clinical flexibility is needed in the real world. It does so by placing responsibility and accountability firmly in the hands of the individual prescriber that, faced with the needs of their patient, are permitted to prescribe off-licence.

A systematic and co-ordinated approach is required both to recognize and develop the evidence base for pharmacotherapy in psychiatry. Key elements of a new model of governance would specifically include the following

1. An extensive, continually updated data resource on the evidence around the off-label use of psychotropics for all patient groups led by the MHRA.
2. Routine documentation of medical indications in the prescribing process, as required practice for clinicians.
3. A research programme, possibly in a new Medical Research Council Centre, and certainly supported by NICE and the Cochrane Collaboration into clinically driven off-label uses, focused on the most regularly prescribed psychotropic medications.
4. Amendments to the licensing process to allow updated good quality evidence from non-RCT research to inform and influence the provisional licensing of add-on indications.

This model of research and prescribing governance would benefit and protect both patients and prescribers, and take forward the contribution of pharmaceutical researchers and manufacturers in a key area of drug repurposing.

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