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Challenges facing primary care in the pharmacological management of major depressive disorder: implications of residual symptoms and functioning

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Background

How to manage patients effectively, efficiently and within resource and budget constraints?

Major depression is the leading cause of ill health and disability worldwide. 2017 marked the year when the World Health Organization led a 1-year global campaign with the goal that more people with depression both seek and get help.[1,2]

In England, Hospital Episode Statistics and Mental Health and Learning Disabilities data sets show that one in three patients with depression are unrecognised. Those who are recognised are often then under-treated, fail to achieve remission and have difficulty returning to full functioning. Both recognised and unrecognised patients with major depressive disorder (MDD) often present in acute care, incurring substantial costs outside secondary mental health (MH) care. Guidelines suggest that most patients with depression disorders should be managed in primary care, rather than by secondary care MH services.[3]

The current focus on service provision for people with MH conditions is concentrated on meeting Improving Access to Psychological Therapies (IAPT) targets, dementia and Early Intervention in Psychosis, Child and Adolescent Mental Health Services, rather than optimising the recognition and management of MDD and identifying factors that predispose to continued illness.

Review and appropriate follow-up of patients with MDD is essential if issues impairing recovery are to be identified and addressed. Within IAPT services, recovery is measured in terms of "caseness": a referral is moved to recovery if the patient was a clinical case at start of treatment ("at caseness") and not a clinical case

at end of treatment.[4] IAPT services also use a unique session-by-session outcome-monitoring system to guide clinicians' choice of procedures and assess the overall outcome of a course of therapy.[5]

Within primary care, the Quality and Outcomes Framework (QOF) rewards practices for provision of "quality care".[6] Under QOF, primary care is only reimbursed for one review of a patient with depression (10–35 days after diagnosis) even though regular review (every 2–4 weeks in the first 3 months and then at longer intervals) is recommended.[6] QOF also encourages clinicians to use self-administered questionnaires, such as the Patient Health Questionnaire (PHQ-9),[7] to identify depression and assess treatment response. In the draft revised NICE depression guidelines, clinicians are encouraged to monitor mood state at regular intervals for patients who continue on medication to prevent relapse, using a formal validated rating scale, eg PHQ-9.[8] However, the value of PHQ-9 to guide prescribing or measure recovery/response to treatment is called into question because patients may not interpret questions in a way that is meaningful to them.[9]

Additionally, within QOF there are no requirements to:

- Differentiate between response and remission: even 50% response or a global assessment is not usually used.
- Determine what "recovery" means: depressive symptoms and/or function?
- Check for residual symptoms:
    - remaining symptoms of initial depression
    - side effects of antidepressant medication

- impact of other co-morbidities/drugs.

- Decide if a patient qualifies for long-term treatment (recurrent depression).

Specific challenges for primary care physicians

The presence of long-term physical illnesses and co-morbid MH disorders may not only mask underlying MDD but also negatively impact on recovery. Even if depression is identified, patients are often reluctant to accept the diagnosis and treatment because of associated stigma. Unrecognised and under-treated MDD results in suffering for the person, their families and friends, poor functioning, often frequent presentations to primary care with apparently minor ailments and inappropriate presentations to acute hospital settings.

Intervention choice depends on several factors: patient choice/acceptability, type and severity of depression, need for rapid treatment effect, prior response to treatment and prevention of relapse. Current practice pays little consideration to residual symptoms and restoration of functioning when choosing an antidepressant. Evidence from the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study highlights that as more treatment steps are required, lower acute remission rates and higher relapse rates occur during the follow-up phase.[10,11]

Which pharmacological treatment, when, in which order or which combination for which patient?

Primary care physicians (PCPs) often treat to a 'NICE Pathway' rather than determining how and where individuals fit into that pathway. For example, patients may be prescribed a selective serotonin reuptake inhibitor (SSRI), even though they have not tolerated or responded to SSRIs previously! A study by Kendrick *et al*

explored the feasibility of using patient-reported outcome measures (PROMs) for monitoring primary care patients with depression.[12] These included Beck Depression Inventory II, Work and Social Adjustment Scale, EuroQol Five-Dimension, Five-Level scale for quality of life and modified Client Service Receipt Inventory for costs. Although patients liked completing PROMs, and this may improve depression outcome, practitioners did not use the results to inform management.

The needs

Even for patients who achieve remission, those with residual symptoms have poorer function and increased risk of relapse.[13] A new approach to decision-making for choosing MDD treatment in primary care is needed. As well as amelioration of depressive symptoms, the aims should be identification of residual symptoms and restoration of normal functioning, so decreasing risk of relapse.[14–17]

A prospective clinical study of primary care patients with MDD, followed for 3 years during subsequent major episodes and episodes of (partial) remission, demonstrated that residual symptoms were common.[18] The most frequently occurring were cognitive impairment, lack of energy and sleep problems, which were present 39–44% of the time during remission. A second study[19] identified cognitive impairment in ~28% of people with unipolar depression.

Some aspects of cognitive impairment may improve with treatment but many patients experience significant problems with attention, executive functioning, immediate recall and processing speed, despite achieving remission.[20] Continued impairment is a risk factor for future depression[14] and associated with poorer response to treatment.

Differential diagnosis of residual cognitive impairment includes co-morbid physical or psychiatric diagnoses, discontinuation syndrome associated with non-compliance, incorrect diagnosis, psychosocial factors, medication side effects and, in older patients, dementia. Because primary care plays a major role in screening for cognitive impairment in people at risk of dementia, clinicians are familiar with identifying these aspects of cognitive impairment but less familiar with the frequent longer-term side effects of commonly prescribed antidepressants (SSRIs and serotonin–noradrenaline reuptake inhibitors): apathy, decreased motivation, fatigue and cognitive dulling.

Residual symptoms should be identified after depressive symptoms have responded to treatment (4–8 weeks) or remitted (6–12 weeks) and other causes have been excluded. A challenge for most PCPs is that they may not understand the various domains of cognitive impairment, such as executive function, working memory, episodic memory, attention and psychomotor processing speed.[20,21]

So what tools are suitable and available to assist PCPs in identifying residual symptoms? The Conradi study used the Composite International Diagnostic Interview (CIDI). Most GPs will not have used the CIDI but will instead be more familiar with tools used to screen for cognitive impairment associated with dementia, not suitable for patients with depression.

In a recent survey, UK PCPs and psychiatrists recognised cognitive dysfunction as an area of unmet need and that there is a lack of objective tests of cognition appropriate for patients with depression that can be easily implemented in primary or secondary care.[22] Currently, there is no consensus about the best tools or test battery to accurately and efficiently assess cognitive impairment associated with depression in

clinical practice. Nor are there data to refute or confirm that the same tools can be used in younger and older adults, male and female.

Equally, there is a paucity of data about how best to manage residual cognitive impairment. Do individual antidepressants differ in their ability to minimise cognitive impairment? Are combinations of drugs, combination drug and psychological therapies or augmentation strategies more effective? Which psychological interventions are appropriate? Should the treatment approach be tailored to the type of cognitive impairment or certain patient characteristics? Concerns have been raised in the past about the increased use of antidepressants, with insinuations that this was inappropriate.[23] An analysis of the national GP research database showed that the increased use was not due to more people receiving antidepressants but rather to more appropriate prescribing in line with national guidelines (6-month minimum recommended treatment rather than 1 month as per previous common practice).[24]

Professionals, patients and politicians need to be reminded that although MDD is labelled as a common MH problem, it has serious health, social and economic consequences. Outcomes after pharmacological treatment should not only target depressive symptoms but also acknowledge the detrimental effect residual symptoms can have on likelihood of full recovery and, like IAPT, focus on restoring function. Consensus is needed regarding identifying residual symptoms, and more research is required about the value of currently available treatments and to identify improved therapeutic strategies.

Conclusion

Depression is the leading cause of disability in the world, achieving this status nearly two decades earlier than predicted. A different management approach is required, with restoration of normal functioning, rather than just remission of depressive symptoms, the goal of treatment. Clinicians, especially those in primary care, need to understand the relationship between residual symptoms and risk of relapse and impaired functioning. Pathways of care should include identification of residual symptoms, especially cognitive impairment, for all patients treated for depression, including those who have remitted. More research is needed to determine the best tools to detect residual symptoms, how best to manage such symptoms and whether the approach should be the same in all patient populations.

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Declaration of interests

Dr Rasmussen is the Clinical Representative for Dementia for the Royal College of General Practitioners; she is Director of her individual consultancy 'psi-napse'. In her consultancy role, she is a past Non-Executive Director for Cerestim and has received payment for consultancy/advisory boards/Speaker Bureaus from Cerestim Ltd, Edmund de Rothschild, Eli Lilly and Lundbeck.

Dr Young has received payment for lectures and advisory boards from all major pharmaceutical companies with drugs used in affective and related disorders; is the Lead Investigator for the Embolden Study (AstraZeneca), BCI Neuroplasticity Study and Aripiprazole Mania Study; investigator-initiated studies from AstraZeneca, Eli Lilly, Lundbeck and Wyeth; and received grant funding (past and present) from NIMH (USA), CIHR (Canada), NARSAD (USA), Stanley Medical Research Institute (USA), MRC (UK), Wellcome Trust (UK), Royal College of Physicians (Edinburgh, UK), BMA (UK), UBC-VGH Foundation (Canada), WEDC (Canada), CCS Depression Research Fund (Canada), MSFHR (Canada) and NIHR (UK). Dr Young is funded by the NIHR: the views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

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