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Review

Risk factors for relapse and recurrence of depression in adults and how they operate: A four-phase systematic review and meta-synthesis

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HIGHLIGHTS

- Prognostic risk factors for recurrence were in order of strength of evidence:
  - 1st: childhood maltreatment, residual symptoms and history of prior episodes
  - 2nd: comorbid anxiety, rumination, neuroticism and age of onset
  - Some also may be prescriptive but evidence for such effects was limited
- Neurocognitive and neuroendocrine factors were identified as potential risk factors
- A conceptual framework considering the risk factors and mechanisms was developed.

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ABSTRACT

Purpose: To review and synthesise *prognostic* indices that predict subsequent risk, *prescriptive* indices that moderate treatment response, and *mechanisms* that underlie each with respect to relapse and recurrence of depression in adults.

Results and conclusions: Childhood maltreatment, post-treatment residual symptoms, and a history of recurrence emerged as strong prognostic indicators of risk and each could be used prescriptively to indicate who benefits most from continued or prophylactic treatment. Targeting prognostic indices or their "down-stream" consequences will be particularly beneficial because each is either a cause or a consequence of the causal mechanisms underlying risk of recurrence. The cognitive and neural mechanisms that underlie the prognostic indices are likely addressed by the effects of treatments that are moderated by the prescriptive factors. For example, psychosocial interventions that target the consequences of childhood maltreatment, extending pharmacotherapy or adapting psychological therapies to deal with residual symptoms, or using cognitive or mindfulness-based therapies for those with prior histories of recurrence. Future research that focuses on understanding causal pathways that link childhood maltreatment, or cognitive diatheses, to dysfunction in the neocortical and limbic pathways that process affective information and facilitate cognitive control, might result in more enduring effects of treatments for depression.

1. Introduction

Depression has the highest disease burden worldwide in terms of life-years lost to disability (Prince et al., 2007). It is highly prevalent, results in significant functional impairment, and increases the risk of suicide and comorbid physical health problems (Judd, 1997; Kessler & Wang, 2009). Recurrence is common in major depression; in non-clinical cohorts a third of all persons who have at least one episode will have another (Eaton et al., 2008) and the same is true for over three-quarters of patients in clinical samples (Mueller et al., 1999). The mean number of episodes per sufferer is approximately four, with a mean duration of approximately 14–17 weeks per episode if mild in severity or 23 weeks if severe (Kessler et al., 2003). While depression traditionally has been seen as an episodic disorder with good inter-morbid functioning (Angst, Kupfer, & Rosenbaum, 1996), it is now thought by many to follow a "relapsing-remitting" course with debilitating subsyndromal symptoms occurring between discrete episodes (e.g. Burcusa & Iacono, 2007).

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1.1. Differentiating remission from recovery and relapse from recurrence

Current convention in the literature is to distinguish between response (better but not fully well) and remission (fully asymptomatic but still in episode) and each from recovery (the resolution of the underlying episode) (Frank et al., 1991). A further distinction is made between relapse (the return of symptoms associated with the remitted episode) and recurrence (the onset of a new episode following recovery) (Rush et al., 2006). Whether these distinctions hold in fact is still not clear but they do guide medication practice as patients are routinely kept on antidepressants (ADM) for up-to a year after reaching remission in order to forestall relapse (Reimherr et al., 1998). What will become clear in the review to follow is that they rarely guide the empirical literature.

Cognitive behaviour therapy (CBT) appears to have an enduring effect that reduces risk for relapse to the same extent as continuation ADM (Cuijpers et al., 2013) and that enduring effect may extend to the prevention of recurrence among recovered patients (Dobson et al., 2008; Hollon et al., 2005). Adding CBT as ADMs are tapered off has also been shown to reduce the risk of subsequent relapse or recurrence (Guidi, Tomba, & Fava, 2015). Even so, current practice is evolving in the direction of keeping patients with a history of recurrent or chronic depression on maintenance medication indefinitely in an attempt to delay or prevent subsequent recurrence (e.g. Thase, 2006). This is despite the suggestion that use of ADM may itself be a factor contributing to the risk of relapse or recurrence (Andrews, Kornstein, Halberstadt, Gardner, & Neale, 2011; Andrews, Thomson, Amstadter, & Neale, 2012; Fava, 2003). It is unclear whether factors other than the duration of remission differentiates those at risk for relapse from those at risk for recurrence (Farb, Irving, Anderson, & Segal, 2015). For that reason we attempt to differentiate between the two in the empirical literature.

1.2. Prognostic versus prescriptive designs and questions

Given that there are different treatment strategies that can be applied and different durations of treatment, the question becomes whether we can identify i) prognostic factors that indicate which patients are at greater risk of relapse or recurrence, and ii) prescriptive factors (moderators) that predict differential response to different treatments thought to help forestall or prevent relapse or recurrence (Fournier et al., 2009). Prognostic indices are best detected when treatment is held constant, ignored, or better still (from the perspective of science) not provided at all and individual differences are allowed to vary. Cohort designs are best suited to answering this question since treatment is not controlled (with those samples that receive the least treatment closest to the "state of nature", and most informative with respect to what factors best predict relapse or recurrence.

Prescriptive designs involve the superimposition of some type of controlled treatment on top of the natural course and their proper interpretation involves testing for patient-by-treatment interactions, but even in controlled trials prognostic indices can be identified too. Within-condition comparisons among patients tells you who is most at risk (prognostic) whereas comparisons between conditions within the same kind of patients tells you what treatment works best for a given kind of patient (prescriptive). The differences in these study designs allow each to answer different albeit overlapping questions. As we shall see, reviews of the empirical literature are not always clear about which type of question is being addressed.

For a fuller explanation of prognostic compared to prescriptive indices see Supplementary Fig. 1.

1.3. Consensus on risk factors for relapse and recurrence

The "consensus view" as defined by Campbell's Dictionary of Psychiatry (2009) and confirmed in individual studies (e.g. Lin et al., 1998) is that two factors influence risk for both relapse and recurrence: 1) residual depressive symptoms at the end of acute treatment, and 2) a prior history of recurrence. It has also been suggested that subsequent episodes become increasingly autonomous from stressful life events (Campbell, 2009), that a lack of social support and social health problems may contribute to risk of relapse (Paykel & Priest, 1992), and that neuroticism and age of first onset are risk factors for recurrence (Gelder, Lopez-Ibor, & Andreasen, 2000). Nonetheless, despite more than half a century of active research into the nature and treatment of depression, we are still unable to predict with confidence who will relapse or recur following treatment termination (Beckerman & Corbett, 2010; Hughes & Cohen, 2009).

One difficulty in identifying more effective approaches to preventing relapse or recurrence is a lack of clarity about what it is that confers risk for each (e.g. Burcusa & Iacono, 2007). A number of studies have been hampered by methodological problems or inconsistencies (Monroe & Harkness, 2011). Early studies did not define relapse and recurrence consistently or failed to distinguish between them altogether (Beshai, Dobson, Bockting, & Quigley, 2011). The majority of more recent studies now follow the conventions set by Frank et al. (1991) and elaborated by Rush et al. (2006), but it is likely that the 8 weeks of continuous remission required by Frank was far too short and that even the 4 month criteria set by Rush may also be too short (Kessler et al., 2003). To the extent that this is true, many apparent "recurrences" would actually be "relapses", making it harder to detect indices that predict differential risk between the two phenomena. In addition, many studies fail to discriminate patients in their first episode from those with a history of multiple previous depressive episodes. Epidemiological studies suggest that as many as half of all people who have an episode of depression will never have another (Eaton et al., 2008) and differences in the case mix across studies can lead to spurious conclusions (Monroe & Harkness, 2011). Studies in clinical samples that suggest that up to 80% of patients will have a recurrence (e.g. Mueller et al., 1999) likely oversample exactly the kinds of chronicity and recurrence that lead people to seek treatment in the first place. Further, the diagnosis of major depressive disorder (MDD) is likely causally heterogeneous. For example, it is given to those who experience prolonged periods of sadness as a reaction to a life event in one-off episodes that frequently remit spontaneously, and to those with chronic, sometimes decades-long episodes that are unresponsive to multiple treatments (Baldessarini et al., 2017; Lorenzo-Luaces, 2015). Such heterogeneity necessarily affects the ability to identify prognostic or prescriptive indices.

Given the methodological difficulties identified, it is not surprising that the field has struggled to determine what predicts risk for relapse and recurrence, whether the risk factors for each are the same or different, whether they are universal to all depression or only particular sub-types, which factors might be prognostic and which prescriptive, and what the mechanisms are by which the risk factors operate (Kazdin, 2007). This review therefore aimed to summarise and synthesise findings from studies that have reported on prognostic and prescriptive risk factors for relapse or recurrence, or that explored the mechanisms underlying the action of each, and how that evidence can guide both clinical practice and future research.

Scoping searches conducted to consider the feasibility of a meta-review of systematic reviews revealed that there were only a handful of systematic reviews of the risk factors for depressive relapse or recurrence, that each was based on only a small number of primary studies, and that very few were reviews of cohort studies. Therefore, it seemed likely that such a meta-review would only elucidate prescriptive effects on risk of relapse or recurrence and not allow us to investigate prognostic effects. Since our aim was to investigate both types of effect a novel approach was indicated. We adopted a phased approach, starting with a meta-review in order to qualitatively synthesise information across a broad literature, looking at all major types of psychiatric and psychological treatment for depression, and including cohorts of depressed participants in all community and health settings. Such meta-