

A REVIEW OF THE EFFICACY AND ROLE OF THE CARD SORT EXERCISE IN THE TREATMENT OF BIPOLAR DISORDER

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SUMMARY

The current card sort exercise described by Agius et al. in 2006 provides a tool for patients and their families to characterise the temporal pattern of occurrence of both stereotyped and idiosyncratic prodromal symptoms that serve as early warning signs predicting a relapse. This 'individual relapse signature' is highly specific for bipolar relapse, and aids identification of a relapse such that patients can be channeled into appropriate early intervention pathways. This review examines the role of the card sort exercise in the treatment of bipolar disorder, and evaluates the evidence for its efficacy.

Few studies involve the card sort exercise, and those that do paired it with other early therapeutic interventions, such that it was difficult to assess the true contribution of the card sort exercise alone to outcome measures such as time-to-relapse or hospitalisation avoidance. We went back to first principles and evaluated the literature concerning various factors necessary for the card sort exercise to be useful. We concluded that there is good evidence that replicable relapse signatures exist as early warning signs for bipolar relapse, and that a certain subgroup of patients and their families can reliably use these signs to seek help and activate therapeutic interventions to abort the relapse episode. Early intervention is both possible and efficacious, which makes early identification of relapse yet more important. The card sort is of less use for depressive relapses, where prodromal symptoms are harder to pinpoint. The card sort exercise is useful in elucidating the relapse signature for each patient, which can then be used in psychoeducation or identification of future relapse episodes. However, more research is needed directly assessing the usefulness of the card sort exercise in helping patients and their families gain insight into the possibility of an imminent relapse.

Key words: bipolar disorder - card sort – prodrome - early warning signs - relapse signatures - relapse prevention - early intervention

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Introduction

Bipolar disorder is a condition characterised by a combination of manic and depressive episodes, and is known to have significant effects on both patients and healthcare providers. In serious cases, it can result in severely compromised quality of life and occasionally even death. Treatments aim to reduce the frequency and severity of relapses in order to improve prognosis and quality of life. There is evidence that early intervention with medication (Agius et al. 2006, Agius et al. 2007) and psychoeducation (Bond & Anderson 2015) whilst the patient is only experiencing prodromal symptoms and has not yet experienced a full blown relapse is able to reduce hospital admissions and lengthen time to relapse.

Card sort exercises help patients and their families characterise patterns of prodromal symptoms unique to the patient that are highly specific for bipolar relapse. These early warning signs often herald a relapse, and identification of these signs allows patients to be channelled into appropriate early intervention pathways.

This paper aims to discuss the development of modern card sorting exercises as a tool for early identification of relapse in bipolar disorder, and to review the evidence for their efficacy in relapse prevention in bipolar disorder.

What is the prodrome to relapse?

There has long been interest in characterising the timeline of bipolar disorder (Carlson & Goodwin 1973), from which evolved a focus on prodromal symptoms, due to their promise for secondary prevention (Molnar et al. 1988). The high relapse rate in bipolar disorder (Judd et al. 2002), and the implications for patients, family, and health and social care uptake, make any potential prodrome worth identifying, as these prodromes may act as early warning signs for relapse. A prodrome can be defined as any symptom, or constellation of symptoms, that signals the impending onset of disease. In the case of bipolar disorder, prodromal symptoms can be stratified into appearing before a manic episode, before a depressive episode, and featuring before either type (Molnar et al. 1988). They can also be stratified as mood and non-mood symptoms. As bipolar disorder is a mood disorder, prodromal mood symptoms can naturally be thought of as subclinical depressive and subclinical mania symptoms. The non-mood symptoms include behavioural, cognitive, neurovegetative, social and other symptoms (Keitner et al. 1996). Finally, they can be divided into classical, stereotyped features that are common to many bipolar patients, or idiosyncratic features that serve as "signatures" for individual patients (Lam & Wong 1997). The integration of all these

perspectives on prodromal symptoms may allow a more complete account of prodromal symptoms in bipolar disorder, and thus allow more precise methods for their detection.

Molnar and colleagues were amongst the first to report a detailed array of prodromal symptoms, with increased activity as a ubiquitous feature of mania prodrome and depressed mood being a near-ubiquitous feature of depression prodrome (Molnar et al. 1988). Overall, mania prodrome features experienced by over 75% of the cohort were elevated mood, behavioural symptoms of increased activity and talkativeness, and neurological symptoms of decreased need for sleep, racing thoughts and increased self-worth. Depression prodrome features experienced by over 75% of those

experiencing depressive episodes were depressed mood and neurological symptoms of decreased energy and concentration ability. Subsequent studies have corroborated these main findings on mood, energy level and sleep changes in both mania and depression prodromes (Lam & Wong 2005, Sierra et al. 2007, Conus et al. 2008, Goossens et al. 2010, Skjelstad et al. 2010, Lobban et al. 2011), also highlighting other features such as increased sociability (Lam & Wong 2005), irritability (Wong & Lam 1999, Conus et al. 2008) and emotional lability (Conus et al. 2008) in mania prodrome and loss of interest (Lam & Wong 2005) and emotional lability (Goossens et al. 2010) in depression prodrome. We have summarised the key prodromal symptoms reported in the literature in Tables 1 and 2.

Table 1. Common prodromal symptoms of manic relapse (%)

	Molnar et al. 1988 N=20 Spontaneous recall	Smith & Tarrrier 1992 N=20 Checklist	Lish et al. 1994* N=500 Spontaneous recall	Wong & Lam 1999 N=206 Spontaneous recall	Egeland et al. 2000* N=58 Spontaneous recall	Goossens et al. 2010 N=112 Spontaneous recall	Lobban et al. 2011 N=93 Checklist	Composite value (%)
Mood								
Euphoria	90	-	-	32	-	-	81	50
Irritability	45	60	9	25	33	-	74	23
Behavioural								
Talkativeness	85	-	-	34	-	-	91	54
Increased activity	100	87	32	45	47	-	87	44
Increased sociability	-	80	-	-	-	16	-	26
Thoughts								
Racing thoughts	80	80	-	29	-	-	87	51
Increased self-worth	75	93	-	-	-	1	46	32
Neurovegetative								
Increased energy	-	87	-	22	-	21	87	39
Decreased sleep	90	80	24	53	26	17	85	37

* Study did not stratify prodrome by mania vs depression

Table 2. Common prodromal symptoms of depression relapse (%)

	Molnar et al. 1988 N=20 Spontaneous recall	Smith & Tarrrier 1992 N=20 Checklist	Lish et al. 1994* N=500 Spontaneous recall	Egeland et al. 2000* N=58 Spontaneous recall	Goossens et al. 2010 N=112 Spontaneous recall	Lobban et al. 2011 N=93 Checklist	Composite value (%)
Mood							
Low mood	86	88	33	53	-	80	44
Irritability	29	-	9	33	-	69	20
Behavioural							
Loss of interest	57	100	-	-	-	84	84
Restlessness	29	-	-	-	-	71	65
Decreased sociability	-	-	-	-	11	85	44
Thoughts							
Negative thoughts	65	-	-	-	-	80	78
Low self-worth	-	100	-	-	2	-	17
Neurovegetative							
Decreased energy	86	82	-	38	12	90	49
Concentration difficulty	79	71	-	-	5	79	43
Decreased sleep	57	-	24	26	10	56	26
Other							
Low motivation	-	-	-	-	-	90	90
Anxiety	-	-	-	22	-	81	58
Guilt	-	-	-	22	-	70	51

* Study did not stratify prodrome by mania vs depression

Stereotyped vs Idiosyncratic

As well as characterising the material symptoms involved in the prodrome to bipolar relapse, a great topic of discussion in the field has been the relative importance of stereotyped features that are common to many bipolar patients, and idiosyncratic features that serve as “signatures” for individual patients (Smith & Tarrier 1992). The former have more readily available tools for identification in each patient, such as psychometric testing, and therefore may serve as a more sensitive measure, whereas the latter may be more specific to each individual. Agius and colleagues describe anecdotally, for example, a woman who would express a wish to travel and to diet two weeks before a full manic relapse (Agius et al. 2007).

The Card Sort Exercise Mechanism

Having discussed the variety of prodromal symptoms that can manifest in bipolar relapse, we now turn to the method for identifying them that is the subject of this paper – the card sort exercise.

The card sort exercise is essentially a means for bipolar patients and their families to identify early warning signs of relapse. A number of different methodologies have been proposed over the years, each based on the idea that individual patients have their own unique set of early warning signs. These methods offer a structured approach for patients to identify their own set of relapse indicators, and thus theoretically increase the likelihood that patients and their families will recognise the early warning signs of relapse when they do arise.

Early descriptions of the card sort exercise favoured the idea of the bipolar prodrome comprising either a stereotyped catalogue of symptoms, or an individualistic idiosyncratic signature (Wong & Lam 1999). More recent descriptions of the exercise however, have recognised the role of both stereotyped and idiosyncratic symptoms in forming a more complete picture of the bipolar prodrome. Birchwood introduced the concept of a timeline covering the weeks leading up to relapse – prodromal symptoms would be retrospectively identified in their correct time period such that patients and their families would, in future, be able to identify both the early warning symptoms for relapse and the time course in which they would be likely to appear (Birchwood et al. 2000).

The current card sort exercise this paper evaluates is based on the system proposed by Agius et al. in 2006. It amalgamates the methods described by various other researchers to create a cohesive four-step process by which relapse indicators can be identified.

Stage 1 – On the day of bipolar crisis when the patient is admitted to hospital in an emergency, the patient is asked to describe signs and symptoms that he or she experienced in the days and weeks leading up to the admission. Patients’ families also help with this if they can, as they may have identified symptoms that the patient didn’t notice themselves.

Stage 2 – The card-sort exercise begins with a set of 100 cards with early warning symptoms inscribed on them, divided into 2 subsets containing symptoms specific for psychosis and mania. The patient is asked to choose cards which contain the symptom(s) he experienced in the lead-up to manic relapse.

Stage 3 – The symptoms identified in Stage 1 which differ from those already on the chosen cards, are inscribed on blank cards and added to the patient’s collection of cards. The patient is then asked to place the symptom cards chronologically on a ‘timeline’ which marks 5 weeks up to and including the relapse point. The investigator makes a note of the chronology and sequence of symptoms to act as early warning signs for manic relapse.

Stage 4 – The 3-stage process is repeated for symptoms experienced prior to a depressive relapse, this time with cards corresponding to psychosis symptoms and depressive symptoms. After the patient’s own relapse indicators are inscribed on the cards, and the cards arranged chronologically on the timeline, the patient is left with a specific relapse signature for both manic and depressive episodes.

Evaluating the Card Sort Exercise

In evaluating the efficacy of card sort exercises in the prevention of relapse of bipolar disorder, a number of factors have to be considered. Firstly, there needs to be established prodromal symptoms or early warning signs associated with mania or depressive relapses – these have already been discussed earlier. Furthermore, such signs must necessarily have a degree of specificity for the relapse condition, as well as be temporally replicable, such that patients and their families can reliably associate these signs with potential relapse. In addition, patients and their families must have the capability to identify these signs. Crucially, the Card Sort exercise must aid patients and their families in this process of identifying relapse signs. Finally, mere identification of early warning signs of relapse is not sufficient; there needs to be proven therapeutic early interventions that follow in order to achieve the end goal of relapse prevention and admission avoidance, otherwise there would be little point in screening for these early warning signs.

The value of the card sort exercise in all this is thus in crystallising the distinct pattern of early warning signs that mark a potential relapse for each individual patient. The use of open questions in the first step (Agius et al. 2006, 2007) means that even idiosyncratic signs unique to the patient can be captured, whilst the use of standard well reported symptoms as prompters in the second stage means that the whole gamut of symptoms experienced are comprehensively collated. These are eventually compiled into a chronological relapse signature personalised for each patient. Hence, the card sort exercises are most efficacious if patients have particular relapse signatures that consistently occur before relapses that patients and their families can pick

up on in order to trigger appropriate help. We thus consider, in turn, the available evidence for all of the factors elucidated above.

Established early warning signs exist heralding bipolar disorder relapse

As established earlier, there is significant evidence that there are recognisable early signs of recurrence in bipolar disorder (Smith & Tarrier 1992, Goossens et al. 2010). A systematic review conducted by Skjelstad and colleagues 2010 showed that the prodrome of bipolar disorder is associated with more or less episodic dysregulation in mood and energy (Skjelstad et al. 2010). Goossens and colleagues suggested that the most commonly seen first symptoms in recurrence are changes in energy level and sleep in mania, as well as change in thought and mood stability in depression (Goossens et al. 2010). The most common prodromal symptoms have been collated into table 2 below.

Considered individually, each prodromal symptom has a low specificity for bipolar relapse (Skjelstad et al. 2010). To improve specificity, Conus et al. (2008) suggested combining prodrome identification with stratification of the patient group by risk factors (Conus et al. 2008). Another solution introduces the concept of an 'individual relapse signature' (Smith & Tarrier 1992), where it is the experience of a constellation of a number of symptoms, in a particular chronological order, that is taken to herald bipolar relapse. Specificity is thus improved, and this is the strategy employed by the card-sort exercise. The evidence suggests that the pattern of prodromal signs and symptoms are unique for each patient (Lam & Wong 1997) as well as to the type of episode (mania/depression) (Perry et al. 1999). Certain patients also appear to display idiosyncratic prodromes that fall outside the commonly defined symptoms (Agius et al. 2007).

These relapse signatures also appear to be temporally replicable. A prospective study by Lam and colleagues (2001) studying 40 bipolar patients over 18 months showed that they were able to report prodromes for both mania and depression with good test re-test reliability (Lam et al. 2001).

Only a proportion of bipolar patients are able to detect prodromes

Detection of early warning symptoms is heavily predicated on the insight of bipolar patients in assessing their own mood and symptoms. In studying the applicability of the self-rated Birchwood insight scale in patients with bipolar disorder, Jónsdóttir et al. (2008) concluded that patients had a relatively high total insight into their own symptoms (Jónsdóttir et al. 2008). A systematic review by Lam & Wong (2005) looking at 6 studies on bipolar prodromes similarly established that despite the small sample sizes in these studies, the finding that bipolar patients can detect prodromes is robust, whilst another systematic review by Jackson et al. (2003) came to a similar conclusion that four out of five individuals with unipolar or bipolar disorder can

identify one or more prodromal symptoms prior to a relapse (Lam & Wong 2005; Jackson et al. 2003). Cross-sectional studies by Mantere et al. (2008) and Goossens et al. (2010) showed that 48% to 56% of the patients studied could identify discrete prodromes occurring before relapse (Goossens et al. 2010; Mantere et al. 2008). This insight is also persistent: Smith and Tarrier (1992) reported that roughly half of their patients were able to maintain such insight all the way until the onset of a full relapse (Smith & Tarrier 1992).

However, there remains a sizeable population of patients who are unable to detect early warning signs (Goossens et al. 2010), or even pinpoint the start of the relapse episode (Mantere et al. 2008). Perhaps this could be attributed to a lack of insight resulting from executive function deficits as part of the pathological process of psychosis (Cooke et al. 2005). Another theory proposed purports that the fluctuating course of the condition and the persistence of residual subacute symptoms following each manic or depressive relapse obscures potential early warning signs and makes them harder to identify (Mantere et al. 2008). Hence, some patients have difficulty delineating when residual symptoms become prodromal symptoms, and when the prodromal symptoms become the full-blown illness (Lam & Wong 2005). There might also be an element of patient denial and refusal to accept that a relapse is imminent, thus voluntarily suppressing identification of these early warning signs (Agius & Oakham 2001).

Given this, the ability of family members to pick up on relapse prodromes becomes even more important. Prodromal symptoms seem to be robust to variation in reporter, with strong correlation between the prodromal symptoms reported by patients themselves compared to those reported by their family members (Keitner et al. 1996). Agius et al. (2006) also report that whilst conducting the card sort exercise on patients and their families, family members were able to identify relapse symptoms that the patients had missed (Agius et al. 2006). However, evidence that family members are good at picking up relapse prodromal symptoms where the patients fell short is scant, and more research is needed (Table 3).

Detecting early warning signs of depression seems to be yet more difficult. The depressive prodrome seems to be shorter than that of mania (Molnar et al. 1988), roughly two weeks as compared to the reported 3-4 week prodrome in mania (Mantere et al. 2008). In addition, whilst prodromal symptoms for mania commonly involve excessive or dramatic behavioural changes, depression prodromes are less distinctive (Altman et al. 1992). Lam and Wong (2005) suggest that early warning signs for depression are more related to a deterioration of normal functioning, such as a loss of interest in work or social relationships, and this may prove harder to pick up (Lam & Wong 2005). Lam and Wong (1997) even reported how some patients spontaneously remarked that depression creeps up on them like a virus, and that "you wake up with it" (Lam & Wong 1997). It is

Table 3. Are bipolar patients able to detect relapse prodromes?

Citation, Study Type and Population	Outcome measure	Key results	Comments
Goossens et al. 2010 Cross-sectional study Cohort of 111 patients with bipolar disorder. Subjects were psychiatric outpatients diagnosed with bipolar I, II or NOS disorder according to DSM-IV-TR criteria, at least 18 years of age, able to complete an interview.	Self-reported: patients were asked to answer the following questions: "How can you tell if an episode of mania or depression is impending?", and: "what is the first sign or behaviour that you recognise in yourself that leads up to a manic or depressive episode?"	44% of patients reported an inability to recognise the symptoms of either an imminent manic or depressive relapse, or both (28% for manic, 28% for depressive, 12% for both). The more depressive episodes a patient had, the more likely they were to recognise their depressive prodromal symptoms. No such association was found for manic prodromes. This may be because prodromal depressive symptoms may be more painful and hence easily recognised than manic prodromal symptoms. It may also be because mania has a greater association with loss of insight than depression. There were no statistically significant associations between the ability to recognise depressive or manic prodromes, and: the number of years since illness onset; the presence of an action plan; previous participation in a psychoeducation course; or living alone.	The authors conclude that their results 'suggest that patients learn to recognise prodromes of recurrence rather by experience than from therapeutic interventions'. This is an important consideration when trying to evaluate the efficacy of tools such as the card-sort, which are predicated on the supposed utility of early intervention in relapse recognition.
Lam and Wong (2001) Prospective study 40 patients with bipolar disorder.	Self-reporting prodromal symptoms, as well as relapse incidence over an 18-month follow-up period.	Bipolar patients were able to report bipolar prodromal symptoms reliably. A quarter of patients reported difficulties in detecting depression prodromes, which tended to be more diverse and consisted of a mix of behavioural, cognitive and somatic symptoms.	
Mantere et al. (2008) Cross-sectional study 191 in-and outpatients, of whom 90 had bipolar I disorder, and 101 had bipolar II disorder.	Self-reporting of the prevalence, type and duration of preceding prodromes, in response to open questions taken from the Jorvi Bipolar Study.	Prodromes were reported by 45.0% of BD I and 50.0% of BD II patients. The first prodromal symptom was usually mood congruent, but sometimes non-specific for mood or a symptom of anxiety; the median duration was 30.5 days.	Cross-sectional studies have limitations in this scenario. If a patient is undergoing a relapse at the time of their interview, their insight into their condition, and hence, their ability to report prodromal symptoms is adversely affected.
Smith and Tarrier (1992) Cohort study 20 patients suffering from manic depressive psychosis	Self-reporting of the symptoms experienced during a manic or depressive prodrome, which were distinct from those experienced during a recent control period during which the patient was in remission.	It was possible for 85% of patients to identify a depressive prodrome and 75% a manic prodrome. 53% of depressive patients and 47% of manic patients reporting that they had full insight into their condition up until the onset of a full relapse. The majority of patients could describe the sequence of events which preceded them losing insight into their condition at the onset of a relapse. The majority of patients (71% for depressive, 73% for manic relapses) could also identify idiosyncratic prodromal symptoms.	
Molnar et al. (1988) Retrospective study 20 patients suffering from bipolar disorder.	Spontaneous recall of the symptoms these patients had experienced during manic and depressive relapse prodromes.	The mean number of days for manic prodromes was 20.5 days, (range 1 to 83 days). The mean number of days for depression prodromes was 11 days (range 2 to 31 days). These patients had considerable inter-individual variability, but very little intra-individual variability of prodromes.	Bipolar patients are better at identifying manic prodromal symptoms than depressive prodromal symptoms. This may be in part due to the increased average length of a manic prodrome. The low intra-patient variability of prodromal characteristics reported strengthens the potential utility of early-intervention methods such as the card-sort.

Table 3. Continous

Citation, Study Type and Population	Outcome measure	Key results	Comments
Keitner et al. 1996 Retrospective study 74 patients suffering from bipolar I disorder.	All 74 patients were asked to recall the symptoms they had experienced leading up to either depressive or manic relapses. In 45 cases, an adult family member was asked to corroborate the patient's reports.	54% of patients described experiencing residual symptoms of depression after their relapse, whilst 68% of patients reported residual manic symptoms. There was a strong degree of agreement between patients and their family members over the prodromal symptoms for both depressive and manic relapses. Cognitive symptoms were the most commonly-reported features of both depressive and manic prodromes.	A high proportion of patients are able to describe their prodromal symptoms accurately, with good corroboration with family observations This proportion is higher for manic prodromes than depressive prodromes.
Altman et al. 1992 Longitudinal study	Mood status was assessed in person using the Brief Psychiatric Rating Scale (BPRS) 2-weeks after discharge, and at months 3, 6 and 9 post-discharge. For months 1,2,4,5,7 and 8, a shorter version of the BPRS was administered via telephone interview.	During the follow-up period, there were six depressive relapses, six manic relapses, and seven non-relapsers. Manic relapsers, unlike depressive relapsers and non-relapsers, reported significantly abnormal thought content, in the form of a sudden mood elevation, one month before relapse. Depressive relapsers reported a significant degree of 'conceptual disorganisation', for an entire 4-month period prior to relapse, which was not seen in manic-relapsers or non-relapsers.	A discrete, acute change in prodromal mood was only really seen in manic-relapsers. Depressive relapses were characterised by more nebulous alterations in cognition over a much longer period. This could mean that attempts to recognise and act upon early relapse indicators, using techniques such as the card-sort, are more likely to be successful for manic rather than depressive relapses.

hence no surprise that bipolar patients are often better at reporting maniac prodromes than depression ones (Molnar et al. 1988, Keitner et al. 1996). It was precisely this difference that led Perry et al. (1999) to conclude that early intervention treatment was effective in reducing maniac relapses but not depressive ones (Perry et al. 1999).

Our conclusion from the literature is that there are a good number of patients who maintain sufficient insight into their symptoms to be able to detect relapse symptoms, and who would thus benefit from the card sort exercise. Methodology papers by Agius et al. (2001) and (2006) showed that patients were seldom able to produce a detailed sequence of early warning signs, even when it appeared likely that such signs were present, but that identification of early warning signs improved greatly when prompted with the card sort exercise (Agius & Oakham 2001, Agius et al. 2006). The card sort exercise facilitates a patient in characterising their relapse signature, as it makes them aware of signs of relapse that they previously did not associate with their disease. Patients and their families can then be on the lookout for these particular symptoms.

Yet, there is another group of patients for whom the card sort will have little benefit. These patients struggle to pinpoint prodromal symptoms or actively deny their existence. Depressive prodromes are also harder to identify, and the usefulness of the card sort exercise might again be limited in these instances.

Identifying early warning signs allows appropriate intervention

Identifying patients at risk of relapse must move on to trigger interventions that can ultimately aid in relapse avoidance. Here, a multiplicity of treatment options has been trialled, all with considerable success. These results have been summarised in the table 4. Agius et al. (2006, 2007) used a combination of motivational interview techniques to promote compliance with medication, stress management and relaxation techniques, behavioural family interventions as well as cognitive behavioural techniques to deal with negative thoughts (Agius et al. 2006, Agius et al. 2007). This culminated in statistically significant reduction in relapses and re-hospitalisation. Colom et al. (2003) and Lam et al. (2003) also showed that psychoeducation techniques were able to significantly reduce the number of both manic and depressive relapses, as well as the number and length of hospital admissions for recurrence. Bond et al. (2015) showed similar outcomes using psychoeducation, in which patients and their families were educated about their illness, early warning signs and management plans with a view to improving their long-term outcome (Bond & Anderson 2015). Miklowitz et al. (2003) also looked at the effect of psychoeducation and early warning sign recognition involving family members (Miklowitz et al. 2003). Patients whose families underwent early warning signs education had a better outcome than those who received crisis management sessions, having a significantly reduced rate

Table 4. Does recognition of early warning signs and therefore early intervention in bipolar patients help to avoid significant relapse?

Paper, study type and study group	Comparison	Outcome measures	Key results	Comments
<p><i>Agius et al. 2006</i></p> <p>Audit</p> <p>N=11 patients with bipolar disorder</p>	<p>Treatment group: Treatment as usual (TAU) with medication, psychoeducation and CBT. In addition to this, the study group were given 'relapse prevention strategies' including work on medication compliance, stress management techniques and EWS recognition, with an agreed relapse prevention plan if EWS detected.</p>	<p>No of hospital admissions</p> <p>Relapse rates</p>	<p>None in treatment group during observation period.</p> <p>Prior to early warning signs work, all relapses had led to hospital admissions.</p> <p>3/11 patients had relapses during a year of observation following EWS education. All relapses treated at home.</p> <p>Prior to early warning signs work, relapse rate ranged from 1 per year to one every 3 years.</p>	<ul style="list-style-type: none"> ▪ Small sample size ▪ Paper assesses the use of the card sort exercise as well as psychoeducation. ▪ It is difficult to assess the true reduction in relapse rates due to the lack of a control group and the potential for error in estimating a predicted relapse rate without EWS intervention. The results do, however, point to a reduction in rates of relapse following EWS psychoeducation. ▪ None of the relapses occurring after EWS education resulted in a hospital admission, which is an important pattern given that all previous relapses had failed to be treated in the home environment. Perhaps EWS education has a role in reducing the severity of relapse even if it is unclear whether it reduces the frequency.
<p><i>Perry et al. 1999</i></p> <p>Single blind RCT</p> <p>N=69 patients with bipolar disorder, who had had a relapse within the previous 12 months</p>	<p>Control group: TAU – routine care delivered by psychiatrists and key workers consisting of drug treatment, monitoring of mood and adherence to treatment, support, education about bipolar disorder and, if necessary, inpatient care.</p> <p>Treatment group: TAU plus 7-12 individual psychoeducation sessions working on recognition of EWS and rehearsal of an action plan if EWS detected.</p>	<p>Time to first manic relapse</p> <p>Number of manic relapses</p> <p>Time to depressive relapse</p> <p>Number of depressive relapses</p> <p>Social functioning</p>	<p>Significantly longer 2^{5th} centile time to first manic relapse: 65 weeks in experimental group compared with 17 weeks in the control group</p> <p>Event curves of time to first manic relapse significantly differed between experimental and control groups, with significant reductions in the number of manic relapses over 18 months.</p> <p>No significant difference in time to first depressive relapse (time to first depressive relapse was 21 weeks in the experimental group and 26 weeks in the control group)</p> <p>No effect on number of depressive relapses</p> <p>Significantly improved overall social functioning and employment by 18 months.</p>	<ul style="list-style-type: none"> ▪ Not double blind – this is difficult (if not impossible) to achieve in psychoeducation trials. ▪ Results point to a significantly reduced rate of manic relapses with EWS education and action plans, but no change in the rate or number of depressive episodes. This may be due to the less obvious nature of EWS prior to depressive relapse, which suggests that whilst EWS recognition might be useful for patients with bipolar before a manic phase, it may not be relevant at all stages of their condition.
<p><i>Miklowitz et al. 2003</i></p> <p>RCT</p> <p>N=101 patients with bipolar disorder (and an episode in previous three months)</p>	<p>Control group: Pharmacotherapy plus 'crisis management intervention' (CM) with family – 2 initial education sessions, then sessions as required to resolve family conflicts.</p> <p>Treatment group: Pharmacotherapy plus 'family-focussed therapy' (FFT). Family members underwent 21 psychoeducation sessions covering EWS recognition and the creation of an action plan for relapse prevention if EWS developed.</p>	<p>Rate of relapse</p> <p>Time to relapse</p> <p>Medication compliance</p> <p>Mood symptoms</p>	<p>Significantly reduced rate of relapse (54% of CM vs 35% FFT, $p < 0.005$)</p> <p>Longer time to relapse</p> <p>Significantly better medication compliance (measured using mean drug adherence scores 0-3, $p = 0.04$)</p> <p>Greater reduction in mood symptoms (based on SAD-C mean total affective symptom score)</p>	<ul style="list-style-type: none"> ▪ Involved family members ▪ 61% of CM patients and 71% of FFT patients continued the trial for the full 24 months. ▪ Not all data are significant ▪ This study suggests that relapse rate is significantly reduced in the context of EWS recognition. The medication compliance of the treatment group was also significantly improved, meaning it is hard to know to what extent EWS work directly prevented relapses and to what extent improved medication compliance accounted for the difference (a possibility explored by the authors themselves).

Table 3. Continous

Paper, study type and study group	Comparison	Outcome measures	Key results	Comments
<p><i>Colom 2003</i></p> <p>Single blind RCT</p> <p>N=120 patients with bipolar I and II disorder who had been relapse-free for 6 months and were receiving pharmacological treatment.</p>	<p>Control group: TAU (regular appointments with psychiatrist and pharmacological intervention) plus 21 sessions of unstructured group meetings</p> <p>Treatment group: TAU plus 21 sessions of group psychoeducation</p>	<p>Number of relapses</p> <p>Time to relapse</p> <p>Number of hospital admissions</p> <p>Length of inpatient stay</p>	<p>Significantly fewer relapses (92% in control experience recurrence vs. 67% in treatment group, $p < 0.001$)</p> <p>Significantly increased time to any relapse episode (manic, depressive or mixed)</p> <p>Significantly fewer hospital admissions over 24 months (mean number of admissions in control group = 0.78 vs treatment group = 0.3, $p < 0.05$)</p> <p>Significantly shorter length of stay per patient (control group = 14.83 days vs treatment group = 4.75 days, $p < 0.05$)</p>	<ul style="list-style-type: none"> ▪ The study design controls for possible supportive effect of group sessions alone, by comparing a structured and unstructured approach. ▪ All these data were significant and supported the notion that psychoeducation alongside TAU could lead to both manic and depressive relapse prevention
<p><i>Lam et al. 2003</i></p> <p>Single blind RCT</p> <p>N=103 outpatients with bipolar I disorder who experienced frequent relapses despite mood stabiliser therapy</p>	<p>Control group: TAU (regular psychiatric follow-up and mood stabilisers)</p> <p>Treatment group: TAU plus 16 sessions of cognitive therapy covering symptoms of bipolar disorder, treatment compliance, EWS recognition and coping strategies if EWS appeared.</p>	<p>Number of relapses</p> <p>Length of relapse episodes</p> <p>Days spent in hospital</p> <p>Depression scores</p>	<p>Significantly fewer bipolar relapses (70% in control group vs. 43.8% in treatment group at 12 months, $p = 0.004$)</p> <p>Significantly fewer days in bipolar episodes ($p = 0.008$)</p> <p>Significantly fewer days spent in hospital (control group = 17.6, treatment group = 10.3, $p = 0.02$)</p> <p>Lower depression scores (Beck Depression Inventory scores, $p = 0.04$ at 6 months)</p>	<ul style="list-style-type: none"> ▪ These data suggest that EWS recognition and the preparation of coping strategies are useful techniques in reducing the rate and severity of bipolar relapses.
<p><i>Rea et al 2003</i></p> <p>RCT</p> <p>N=53 patients with bipolar disorder I recently hospitalised for manic episode, all on mood stabilisers</p>	<p>Control group: Pharmacotherapy plus 21 individual patient sessions including psychoeducation about the condition, awareness of symptoms, reduction of ongoing life stress and crisis management</p> <p>Treatment group: Pharmacotherapy plus 21 family focussed therapy (FFT) sessions including psychoeducation about symptoms and treatment of bipolar disorder, communication training, problem solving and EWS recognition with relapse prevention plan if EWS detected</p>	<p>Number of hospitalisations</p> <p>Number of relapses</p> <p>Likelihood of first relapse</p> <p>Time to relapse</p>	<p>Fewer hospitalisations</p> <p>Significantly fewer relapses</p> <p>No significant difference</p> <p>No difference in time to relapse</p>	<ul style="list-style-type: none"> ▪ Involved family members ▪ Small sample size for the comparison of two psychoeducational strategies ▪ Although there was no difference in time to relapse, the treatment group had significantly fewer hospitalisations around the time of relapse as compared to the control group. Perhaps a combination of family group therapy and individual EWS psychoeducation could be helpful in reducing both admissions and relapse rate.
<p><i>Jones & Burrell-Hodgson 2008</i></p> <p>Prospective non-controlled study</p> <p>N=7 outpatients recently diagnosed with bipolar disorder I. 6/7 patients were receiving pharmacotherapy at the time</p>	<p>Treatment group: 14-18 sessions of cognitive behavioural therapy (CBT) including education about bipolar disorder, detection of EWS, application of coping mechanisms when EWS recognised to reduce the risk of relapse and stabilisation of sleep and behaviour</p>	<p>Prodromal identification – mania</p> <p>Prodromal identification - depression</p>	<p>Participants reported significantly more mania</p> <p>prodromes and adaptive coping strategies for mania at end of treatment compared with baseline with large effect sizes in both cases.</p> <p>Number of identified prodromal signs of depression increased between baseline and end of follow-up.</p>	<ul style="list-style-type: none"> ▪ Not RCT – difficult to assess exact effect of EWS education ▪ Small sample size ▪ Study looked at the combined effect of CBT with EWS psychoeducation, and intervention early on in the disease course. It is therefore difficult to distinguish the effect of each factor. ▪ No data on relapse recurrence rates, but does suggest that patients can identify prodromes more effectively.

Table 4. Continous

Paper, study type and study group	Comparison	Outcome measures	Key results	Comments
<i>Bond et al. 2015</i> Systematic review of RCTs 16 RCTs included	Control group: Placebo control (e.g. individual psychoeducation compared with group psychoeducation) or TAU (psychiatric review and pharmacotherapy) Treatment group: TAU (psychiatric review and pharmacotherapy) plus psychoeducation about bipolar disorder (some with EWS recognition work)	Number of manic or depressive relapses Number of manic/hypomanic relapses Number of depressive relapses Medication adherence Mood symptoms, quality of life and functioning	Psychoeducation appeared to be effective in preventing any relapse (pooled control =30% did not relapse vs. pooled treatment group =45% did not relapse. Significant difference, data heterogeneous) Appeared to be effective in preventing manic or hypomanic relapse (pooled control =54% did not relapse vs. pooled treatment group =69%. Not significantly different, data heterogeneous) Psychoeducation not effective in reducing depressive relapses (data heterogeneous) Psychoeducation improved medication adherence (data heterogeneous) No consistent effects on mood symptoms, quality of life, or functioning were found	<ul style="list-style-type: none"> ▪ Heterogeneous data must be treated with caution ▪ Some studies compared the impact of group psychoeducation vs. individual psychoeducation, and not specifically EWS prevention, so not all studies relevant here. ▪ There is a definite suggestion that psychoeducation about bipolar disorder (with or without EWS recognition) can reduce the rate of manic relapse, however the effect on the rate of depressive episodes is again unclear. This suggests that depressive episodes are less well prevented by EWS than manic episodes, and perhaps that psychoeducation has a place in the management of bipolar disorder, but requires further support in preventing depressive relapse.
<i>Morriss et al. 2007</i> Cochrane review 11 RCTs included, all patients diagnosed with bipolar disorder	Control group: TAU (psychiatric review and pharmacotherapy) Treatment group: TAU plus at least one hour of individual or group-based EWS recognition and management training (ranging from 5 – 21 sessions). Interventions upon recognition of EWS included cognitive therapy, urgent referral to healthcare professional and family therapy sessions.	Time to relapse Time to manic/hypomanic episode Time to depressive episode Percentage of patients hospitalised	6 studies reported time to relapse. The pooled estimate was significant favouring the EWS intervention group, but the results showed heterogeneity (hazards ratio 0.57, 95% CI 0.39 to 0.82) 4 trials reported time to manic/hypomanic episode. The pooled estimate was almost significant favouring the EWS intervention group, but the results showed heterogeneity (hazards ratio 0.66, 95% CI 0.40 to 1.06) 4 trials reported time to depressive episode. The pooled estimate was significant favouring the EWS intervention group, but the results showed heterogeneity (hazards ratio 0.57, 95% CI 0.33 to 0.99) 4 studies reported percentage of patients hospitalised. The pooled estimate was significant favouring the EWS intervention group, and the results showed little heterogeneity (RR 0.67, 95% CI 0.47 to 0.95)	<ul style="list-style-type: none"> ▪ No studies found comparing effect of intermittent medication use when EWS identified vs. TAU and continual medication use, as opposed to continued pharmacotherapy use seen in all other papers included above. ▪ Not all data significant ▪ There was heterogeneity throughout the data, however trends did suggest that EWS recognition allowed for an increased time to relapse (both manic and depressive), and a reduction in the number of patients hospitalised as a result.

of relapse and significantly improved medication compliance. Rea et al. (2003) carried out similar research, finding that patients who received psychoeducation including early warning sign recognition and management had significantly fewer relapses and fewer hospital admissions for bipolar episodes (Rea et al. 2003). A Cochrane review by Morriss et al. (2007) showed an overall beneficial effect of early intervention on the basis of early warning symptoms on time to recurrence, percentage of people hospitalised and functioning in people with bipolar disorder (Morriss et al. 2007).

However, such positive results do not always carry over to depressive relapse avoidance. Perry et al. (1999) reported that their experimental treatment involving

early warning signs education and the development of an action plan in the event of early warning signs recognition was effective only in reducing the rate of manic relapse and not that of depressive episodes (Perry et al. 1999). Bond et al. (2015) likewise concluded that there was less certainty that psychoeducation was effective in preventing depressive relapses (Bond & Anderson 2015). Jones and Burrell-Hodgson (2008) assessed the effect of psychoeducation including early warning sign recognition on patients' ability to identify manic and depressive prodromal symptoms (Jones & Burrell-Hodgson 2008). They found that whilst patients reported significantly more manic prodromes, the increase in depressive prodrome reporting, though present, was not

significant. This suggests that early warning sign education is more effective in increasing patients' awareness of manic prodromes and may therefore explain the reduced impact of early warning signs recognition on depressive relapses. This relative difficulty in recognising depressive warning signs combined with the shorter prodromal lead time of depressive episodes leaves less time for successful early intervention.

Conclusion

The usefulness of the card sort exercises lies in its ability to elucidate the relapse signature unique to each patient, thereby affording mental health workers a platform to comprehensively capture both the idiosyncratic patient-specific symptoms as well as more common prodromal symptoms that the patient experiences, in a chronological fashion, and to identify these symptoms in the future to spot risk of bipolar relapse.

Studies evaluating the efficacy of the card sort exercises should thus compare ability of patients and their families at identifying early warning signs with and without undertaking a card sort exercise. However, there is a lack of research that primarily investigates the efficacy of the card sort exercise in achieving clarity in relapse signature identification; in all studies that involved the card sort exercise it was paired with other therapeutic interventions, and the outcomes measured related to downstream goals such as relapse and hospitalisation avoidance as well as severity of relapse (Agius et al. 2006, 2007). Whilst Agius' findings were strongly supportive of using the card sort exercise and intervening early, it was hard to delineate just how much the card sort exercises contributed to these positive findings. Furthermore, these studies were small and unblinded; there is definitely a need for more research in this area, and especially research specifically comparing prodromal symptom identification in patients using the card sort exercise versus a control group that simply presented when they felt that they were on the verge of a relapse.

However, in evaluating the existing literature we have also shown that there is good evidence that replicable relapse signatures exist as early warning signs that a bipolar relapse is imminent, and that at least a certain subgroup of patients and their families can reliably use these signs to seek help and activate pharmacological, psychological or behavioural modification therapy to attempt to abort the relapse episode. Furthermore, early intervention is both possible and efficacious, albeit more so for maniac relapses than depressive ones. Hence, reasoning from first principles, we argue that the card sort process can contribute to this process beneficially by crystallising the relapse signature. We believe that whilst more research is needed, there is great potential for the card sort exercise to be introduced in relapse monitoring in bipolar disorder, and especially in the avoidance of mania relapses.

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All authors wrote individual parts of the article, which were then edited together.

Mark Agius conceived the project, supervised the project and did corrections.

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