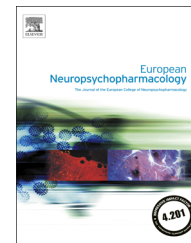




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## REVIEW

# Experience sampling and ecological momentary assessment studies in psychopharmacology: A systematic review

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## Abstract

Experience sampling methods (ESM) and ecological momentary assessment (EMA) offer insight into daily life experiences, including symptoms of mental disorders. The application of ESM/EMA in psychopharmacology can be a valuable addition to more traditional measures such as retrospective self-report questionnaires because they may help reveal the impact of psychotropic medication on patients' actual experiences. In this paper we systematically review the existing literature on the use of ESM/EMA in psychopharmacology research. To this end, we searched the PsycInfo and Medline databases for all available ESM/EMA studies on the use of psychotropic medication in patients with DSM-III-R and DSM-IV disorders. Dissertations were excluded. We included 18 studies that applied ESM/EMA to study the effects of medication on patients with major depressive disorder, substance use disorder, attention-deficit hyperactivity disorder, psychotic disorder, and anxiety disorder. We found that ESM/EMA may allow researchers and clinicians to track patients during different phases of treatment: before treatment to predict outcome, during treatment to examine the effects of treatment on symptoms and different aspects of daily life experience, and after treatment to detect vulnerability for relapse. Moreover, ESM/EMA can potentially help determine how long and in what contexts medications are effective. Thus, ESM/EMA may benefit both researchers and clinicians and might prove to be an effective tool for improving the treatment of psychiatric patients.

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## 1. Introduction

Retrospective clinician-administered and self-report questionnaires are the golden standard in human psychopharmacology. Usually, to evaluate treatment progression and outcome in clinical practice and randomized controlled trials, past symptoms are assessed over a period of several days or weeks. However, this golden standard is not undisputed (Moskowitz and Young, 2006). Retrospective measures are subject to memory distortions. They reveal how patients have reconstructed the past, not how they were experiencing it in situ (Reis, 2012). In contrast, experience sampling methods (ESM) and ecological momentary assessment (EMA) enable clinicians and researchers to tap into daily life processes in real time. The importance of ESM/EMA to capture the daily experience of symptoms is increasingly being recognized in psychiatric research (Myin-Germeys, 2012). Consequently, we believe the time has come to systematically review ESM/EMA studies on the pharmacological treatment of patients diagnosed with a mental disorder.

### 1.1. Advantages of ESM/EMA for the field of human psychopharmacology

As mentioned above, one advantage of ESM/EMA for the field of human psychopharmacology is the reduction in memory bias. Retrospective questionnaires are well-suited when clinicians evaluate how patients experienced treatment after the treatment has been completed. However, patients' reflections on past experiences may not correspond with actual experiences during treatment. For example, current mood influences the type of information that is recalled (Koster et al., 2010). Additionally, Barge-Schaapveld and Nicolson (2002) studied depressed individuals and reported low agreement between side effects recorded in real time using ESM/EMA and side effects reported to a general practitioner. This is highly relevant to psychopharmacology, as it implies that side effects may

lead to treatment discontinuation even when they are not recognized as such by the prescribing clinician. Further, retrospective recall of average levels of mood or symptoms might be more difficult than considering the present moment, particularly for individuals with psychiatric diagnoses (Myin-Germeys, 2012). Furthermore, retrospective recall of *fluctuations* in mood or symptoms is highly unreliable. For example, Solhan et al. (2009) found that retrospective reports of extreme mood changes, over the previous month and even over the preceding week, were largely unrelated to reports obtained in situ. As ESM/EMA questions pertain to the present moment or to a recent interval, memory biases are expected to be minimal.

A second advantage of ESM/EMA is that it taps into processes and experiences as they occur in real life. As a result, the conclusions drawn from psychopharmacology studies that used ESM/EMA are highly ecologically valid (Reis, 2012). In contrast, measurements obtained in laboratory settings may not always generalize to daily life. The relevance for the field of human psychopharmacology is exemplified by a recent study which found highway driving performance, assessed in situ using a specially outfitted vehicle, to remain impaired 3-4 h after intake of zolpidem (Vermeeren et al., 2014), even though laboratory tests conducted at this time no longer indicate any deficiencies Roth et al., 2008.

Third, when ESM/EMA is used to test the effects of a pharmacological agent, these effects are assessed repeatedly, at different times and in different situations. Thus, ESM/EMA can provide psychopharmacologists with valuable information regarding patients' treatment response in multiple relevant contexts. This information can even be offered as feedback to individual patients (Wichers et al., 2011a). Providing patients with insight into how their feelings, thoughts, and behaviors are influenced by contextual factors enhances control over their treatment process and prognosis.

Finally, ESM/EMA offers methodological flexibility such that it can be tailored to the research or clinical question at hand. By using signaling devices, participants can be asked

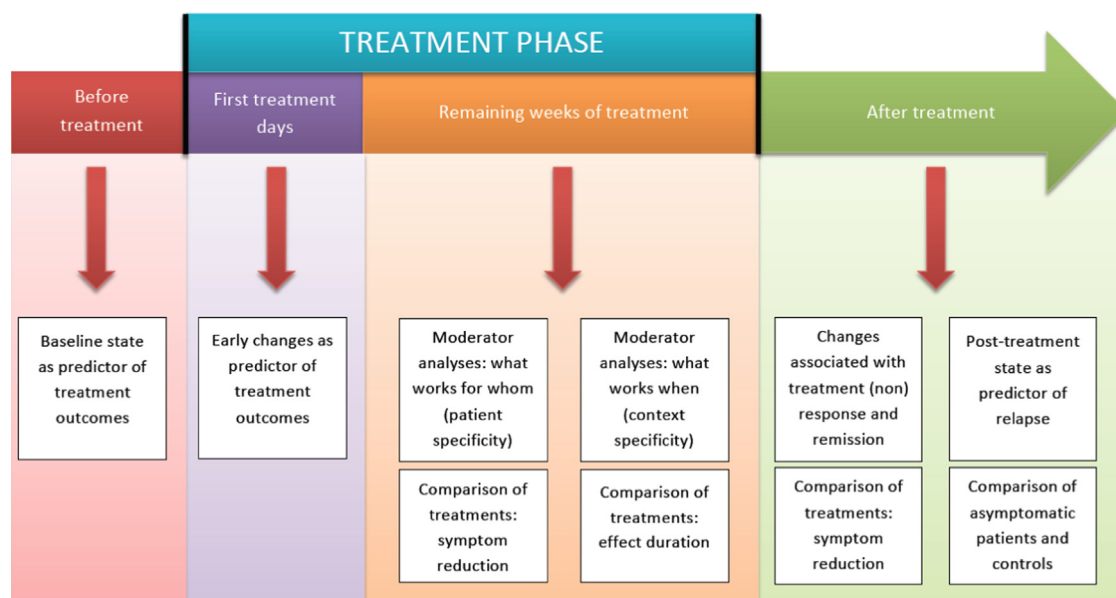


Fig. 1 The value of ESM/EMA in different phases of treatment.

**Table 1** Overview of included studies.

Patient group		Design	Comparison group(s)		Measurement method					Population	
N	Medication (n)		N	Description	Format	Contingency	Observations per day	Days	Observations	Compliance	
<i>Major depressive disorder</i>											
Barge-Schaapveld and Nicolson (2002) <sup>a</sup>	63	Imipramine (32) or placebo (31)	B	22 Healthy	Paper	Signal	10	21	210	At least 50%, for 80% of included patients	Adult
Barge-Schaapveld et al. (1995)	21	Fluvoxamine (11) or amitriptyline (10)	B & W	- -	Paper	Signal	10	12	120	On average 81%	Adult
Geschwind et al. (2011) <sup>a</sup>	63	Imipramine (17) or placebo (22)	B	- -	Paper	Signal	10	9	90	At least 50%, for 80% of included patients <sup>**</sup>	Adult
<i>Höhn et al., 2013</i>											
Study 2 <sup>b</sup>	43	Serotonergic antidepressants*	W	39 Healthy	Paper	Signal	10	6	60	On average 82% <sup>**</sup>	Adult
Study 3 <sup>a</sup>	50	Imipramine (23) or placebo (27)	B	21 Healthy	Paper	Signal	10	6	60	At least 50%, for 80% of included patients <sup>**</sup>	Adult
Peeters et al., 2010 <sup>b</sup>	43	Serotonergic antidepressants*	W	39 Healthy	Paper	Signal	10	6	60	On average 82%	Adult
Wichers et al. (2009) <sup>a</sup>	63	Imipramine (32) or placebo (31)	B	22 Healthy	Paper	Signal	10	9	90	At least 50%, for 80% of included patients <sup>**</sup>	Adult
Wichers et al., 2011b	47	Serotonergic antidepressants*	W	39 Healthy	Paper	Signal	10	6	60	On average 82% <sup>**</sup>	Adult
<i>Substance use disorders</i>											
Cooney et al. (2007)	118	Nicotine patch + intensive smoking cessation treatment (55) or brief smoking cessation advice intervention only (63)	B	- -	PDA	Signal Event	4 Variable?	14 14	52 Variable	On average 73%	Adult

Table 1 (continued)

	Patient group		Design	Comparison group(s)		Measurement method					Population
	N	Medication (n)		N	Description	Format	Contingency	Observations per day	Days	Observations	
Holt et al. (2012)	48	Nicotine patch + nicotine gum or nicotine patch + placebo gum	B	- -	Phone	Signal	5	28	140	On average 65%	Adult
Muhonen et al. (2008)	80	Memantine (40) or escitalopram (40)	B	- -	Paper	Event	Variable	182	Variable	-	Adult
Tidey et al. (2008)	173	Naltrexone (88) and placebo (85)	B	- -	PDA	Signal Event Time	5 1 4	33 33 33	165 33 132	On average 79%	Adult
<i>Attention-deficit hyperactivity disorder</i>											
Gehricke et al. (2006)	10	1. Nicotine patch 2. Nicotine patch + stimulant medication [Dexedrine (2); Ritalin (2); Adderall (3); Concerta (3)]; 3. Placebo patch + stimulant medication; 4. Placebo	W	- -	PDA	Signal	25-30	8	200-240	Unknown	Adult
Gehricke et al. (2011)	15	Individualized ADHD medication [Dextroamphetamine (1); Amphetamine (7); Atomoxetine (4); OROS-Methylphenidate (1); Lisdexamphetamine (2)] and placebo	W	- -	PDA	Signal Event	~9 ~13	4 4	Variable Variable	Unknown	Adult
Whalen et al. (2010)	51	Stimulant medication (26) or atomoxetine (25)	B	58 Healthy	PDA	Time	2	7	14	Unknown	Child and adolescent
<i>Psychotic disorders</i>											
Lataster et al. (2011a)	13	Aripiprazole while discontinuing dopamine antagonists	W	- -	Paper	Signal	10	12	120	On average 71.5%	Adult
Lataster et al. (2011b)	109	Haloperidol (39), risperidone (35), or olanzapine (35)	B	- -	Paper	Signal	10	6	60	Unknown	Adult
<i>Anxiety disorders</i>											
Forbes et al. (2012)	66	SSRI (21), CBT + SSRI (21), or CBT (24)	B	- -	Phone	Signal	2-4	20	60-80	On average 88.5%	Child and adolescent
Sheehan et al. (2007)	30	Alprazolam-CT and Alprazolam-XR	W	- -	Paper	Time	24	63	1512	Unknown	Adult

Note: Studies consisting of at least partly of the same individuals are marked with identical superscript letters. B=between subjects design; W=within subjects design; PDA=personal digital assistant, handheld computer or smartphone; Phone=phone call; D-AMPH=Dextroamphetamine; Alprazolam-CT=compressed tablet; Alprazolam-XR=extended release.

\*Supplemented with supportive psychotherapy.

\*\*Compliance data for this study was not mentioned but considered similar to other studies reporting on the same sample.

to provide recordings or assessments at unpredictable intervals. This signal-contingent approach aims to increase insight in ongoing daily-life processes, such as fluctuations in mood or physiology (Wilhelm et al., 2012). Other approaches sample at specific times of the day (i.e., time-contingent recording; Conner and Lehman, 2012) or in proximity of events of interest such as cigarette smoking (i.e., event-contingent recording; Moskowitz and Sadikaj, 2012). Early ESM/EMA studies used paper questionnaires, but computerized versions on personal digital assistants (PDAs) and smartphones have also become available. Thus, it is increasingly interesting for experimental psychopharmacologists to incorporate ESM/EMA into their research, and for clinical psychopharmacologists to incorporate ESM/EMA into their treatment.

## 1.2. The present review

ESM/EMA has been used extensively in psychiatry. This indicates that the intensive sampling procedure of ESM/EMA can provide reliable and valid data in patients with severe mental illness. For example, there are reviews on ESM/EMA studies on major depressive disorder (MDD; aan het Rot et al., 2012), psychotic disorders (Oorschot et al., 2009), substance use disorders (Shiffman, 2009), anxiety disorders (Walz et al., 2014), and eating disorders (Haedt-Matt and Keel, 2011). However, no previous review has focused on the use of ESM/EMA in psychopharmacology across disorders. Here we review how ESM/EMA has been used in studies that involved psychopharmacological treatment of patients with Axis I diagnoses according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association, 2000). We describe how ESM/EMA has been applied before, during, and after treatment to enhance insight into predictors of treatment outcomes, processes of change, and residual symptoms. We subsequently discuss how these various uses of ESM/EMA can be applied across disorders in future studies and how psychopharmacology might benefit from using ESM/EMA along more traditional measurement approaches.

## 2. Experimental procedures

We searched the online PsycInfo and Medline databases, which yielded 1919 potentially relevant studies in our final search (August 2015). Our search terms can be found in Supplementary Table 1. Subsequently, FB and MahR independently reviewed the titles, abstracts, and full articles sequentially, while applying the following selection criteria: (1) examination of a pharmacological intervention; (2) repeated measures took place outside the laboratory more than once a day for at least 24h; and (3) DSM-III or DSM-IV diagnoses were established using validated clinical instruments. The PRISMA guidelines were followed during the search for and selection of studies (Moher et al., 2009). Initial disagreements regarding the final selection were resolved by reaching consensus. Reference lists of the selected articles were inspected to determine whether eligible studies had been missed. We also examined the digest of the website of the Society of Ambulatory Assessment. We excluded dissertations and studies not published in English. Supplementary Fig. 1 includes details on the reasons for exclusion on the basis of the abstracts and the full articles.



**Table 2** Terms used in ESM/EMA studies on major depressive disorder.

Term	Definition	Operationalization
Dynamic interplay between negative and positive emotions (Wichers et al., 2012)	Decreased negative affect after increases in positive affect	Course of negative affect one beep before and five beeps after the maximum within-person increase in positive affect per day
Emotional reactivity (Peeters et al., 2010)	Reacting with increased positive affect or negative affect to positive or negative events, respectively	Predictive value of affective response after a positive or negative event at the same beep
Retention of positive affect (Höhn et al., 2013)	Ability to savor positive affect for longer periods of time	Value of positive affect at the previous beep in predicting positive affect at the next beep
Reward experience (Wichers et al., 2009)	Increased positive affect after positive events	Effect of positively appraised events (events that are enjoyable, do not require effort and that the participant is skillful at) on positive affect
Stress sensitivity (Wichers et al., 2009)	Increased negative affect after stressful events	Effect of stressful events (events that are not enjoyable, require effort, and that the participant is not skillful at) on negative affect

Note. ESM/EMA=Experience sampling methods/Ecological momentary assessment.

### 3. Results

Table 1 provides an overview of the 18 selected studies. They are concerned with the treatment of MDD, substance use disorders, attention-deficit hyperactivity disorder (ADHD), psychotic disorders, and anxiety disorders. While we set out to include ESM/EMA studies on all DSM-IV Axis I disorders, there were no eligible studies for most disorders.

Sample sizes of the selected studies ranged from 10 to 173 patients. Compliance with the ESM/EMA procedures was unknown for five studies but otherwise considered adequate. Most studies included affect variables as a proxy of mood state, with items such as happy, pleased, and excited

reflecting positive affect and items such as sad, anxious, and angry reflecting negative affect.

#### 3.1. Major depressive disorder (MDD)

Most of the selected studies were conducted in patients with MDD. One study examined youth with MDD and/or an anxiety disorder. This study is reviewed under anxiety disorders.

There are seven MDD studies in adult populations. These studies were all conducted in one of three samples. Sample 1 included 49 first-episode and recurrently depressed individuals who were treated with monoaminergic antidepressants in a flexible dose and received supportive psychotherapy. ESM/EMA was conducted for six days prior to the start of treatment. Follow-up data (no ESM/EMA) were collected 1, 2, 3, 6, 12, and 18 months afterwards. Sample 2 included 63 currently depressed individuals treated with the tricyclic antidepressant imipramine or placebo. ESM/EMA was conducted for six days prior to the start of treatment, for the last three days of the first week of treatment, and for six days after six weeks of treatment. A subgroup of patients also provided follow-up ESM/EMA data at 18 weeks after the start of treatment. Finally, Sample 3 consisted of 21 MDD patients randomized to fluvoxamine or amitriptyline. Patients completed ESM/EMA procedures for six days before the start of treatment and for another six days after six weeks of antidepressant treatment. The researchers who studied Samples 1 and 2 operationalized several concepts related to mood, which are summarized in Table 2.

Samples 1 and 2 have both been used to study associations between baseline affect dynamics and treatment outcomes. Using Sample 1, Peeters et al. (2010) examined emotional reactivity to daily events (cf. Table 2) before treatment as a predictor of depression severity after treatment. Importantly, the predictive value of emotional reactivity was tested after first including traditional clinical predictors of MDD course in the statistical model. Peeters et al. (2010) also examined baseline stress sensitivity (Table 2) as a predictor of remission. Similarly, Wichers et al. (2012) examined in Sample 1 the “dynamic interplay between negative and positive emotions” at baseline as a predictor of MDD course, treatment response, and remission. Additionally, baseline retention of positive affect (cf. Table 2) was examined as a predictor of treatment response in both Sample 1 and Sample 2 (Höhn et al., 2013).

Sample 2 has additionally been used to examine early responses after several days of treatment as predictors of treatment response and outcome. Barge-Schaapveld and Nicolson (2002) examined side effects in the first treatment week as a predictor of dropout after six weeks. Geschwind et al. (2011) examined changes in positive and negative affect levels during the first week of treatment as a predictor of depressive symptoms on the Hamilton Depression Rating Scale (HDRS), treatment response, and remission. As with the Peeters et al. (2010) study, the predictive value of early changes in positive affect was tested after including traditional clinical predictors of MDD course in the statistical model.

Finally, Samples 2 and 3 have been used to study treatment outcomes. Barge-Schaapveld et al. (1995) compared in Sample 3 the effects of successful and unsuccessful

antidepressant treatment on mood and on passive versus active time expenditure (i.e., reading or doing nothing versus engaging in sports or hobbies, respectively). In Sample 2, [Wichers et al. \(2009\)](#) studied treatment-induced changes in stress sensitivity and reward experience (see [Table 2](#)). In the same sample, [Barge-Schaapveld and Nicolson \(2002\)](#) examined the effects of antidepressant treatment on quality of life, mood, and enjoyment of activities. ESM/EMA was able to distinguish between remitted patients and healthy controls after 18 weeks of treatment, whereas the HDRS no longer indicated any differences.

In sum, past studies on the pharmacological treatment of MDD have used ESM/EMA in different phases of treatment: (1) before treatment to predict which patients will respond favorably; (2) early in treatment to detect the first changes in affect regulation, which may help predict later outcome; and (3) after treatment to study the effect of treatment on symptomatology and to differentiate between responders and nonresponders and between remitted patients and healthy individuals, which may help predict which patients are likely to relapse. Moreover, ESM/EMA may be a predictor of depressive symptoms above and beyond traditionally used depression measures.

### 3.2. Substance use disorders

Pharmacological treatment for substance use disorders has been investigated in four ESM/EMA studies. Two studies focused on alcohol dependence. [Muhonen et al. \(2008\)](#) compared memantine to escitalopram in alcohol-dependent patients with comorbid MDD and used event-contingent recording to collect real-time data on alcohol consumption. No other ESM/EMA data were collected.

[Tidey et al. \(2008\)](#) studied the effects of naltrexone in heavy drinkers, of whom more than one-third were diagnosed with alcohol dependence. ESM/EMA was conducted for one week before and for four weeks after the start of treatment. Patients recorded drinking urges, mood, situational variables, and the effects of alcohol. The data were used to examine the effects of naltrexone on the percentage of drinking days, the amount of time between drinks, the intensity of drinking urges, and the stimulating effects of alcohol. Further, the authors conducted moderator analyses to examine the effects of naltrexone on specific subgroups (i.e., gender, genetic subtypes, early onset versus late onset drinkers, patients with versus without a family history of alcohol problems).

The other two studies focused on concurrent alcohol and nicotine dependence. [Holt et al. \(2012\)](#) studied patients with alcohol or dependency and nicotine dependency. Patients were given a nicotine patch and additionally randomized to nicotine gum or placebo gum. ESM/EMA was conducted for one month during treatment. [Cooney et al. \(2007\)](#) also examined concurrent alcohol and nicotine treatment in patients enrolled in an intensive substance abuse treatment program. Patients were randomized to a smoking cessation intervention, consisting of behavioral counseling and transdermal nicotine replacement, or to brief smoking cessation advice. ESM/EMA was conducted for two weeks post-treatment. In both studies, ESM/EMA was used to assess smoking and drinking urges and behavior, mood, and abstinence self-efficacy (i.e., the

confidence to resist drinking and smoking urges). Both studies used ESM/EMA data to identify both risk and protective factors for smoking and alcohol relapse in patients' natural environments, during treatment ([Holt et al., 2012](#)), and after treatment ([Cooney et al., 2007](#)).

In sum, ESM/EMA studies of pharmacological treatment in substance use disorder have shown ESM/EMA can be used (1) to estimate the number of drinks consumed during the day, (2) to reveal what types of patients benefit the most from a particular medication by studying moderation effects, and (3) to prospectively study antecedents of smoking and drinking lapse in the preceding hours, in the presence of patients' own smoking and drinking cues and situations, in different phases of treatment.

### 3.3. Attention-deficit hyperactivity disorder (ADHD)

There have been two ESM/EMA studies on the treatment of ADHD in adults ([Gehricke et al., 2006, 2011](#)) and one in youth [Whalen et al. \(2010\)](#).

[Gehricke et al. \(2006\)](#) examined the effects of four pharmacological interventions in adult smokers with ADHD: a transdermal nicotine patch or a placebo patch with or without stimulant medication (details in [Table 1](#)). ESM/EMA was used during each intervention to monitor ADHD symptoms and a self-defined core symptom, which was daydreaming for 50% of patients and zoning out for the rest. The authors examined the effects of the four two-day interventions on core symptoms, mood, arousal, self-control, and smoking urges.

In a second study, [Gehricke et al. \(2011\)](#) compared the effects of ADHD medication (see [Table 1](#)) and placebo on smoking and withdrawal symptoms. Patients recorded ADHD symptoms, smoking urges, and stress levels for two days during both interventions. In addition to the effects of medication on symptoms and smoking, the authors studied in which contexts the medication was most effective.

[Whalen et al. \(2010\)](#) compared atomoxetine to stimulant medication in children with ADHD. The ESM/EMA questionnaires were completed in the mornings and evenings by the children's mothers and assessed the mothers' moods as well as their perceptions of the moods and behaviors (e.g. inattention, hyperactivity, impulsivity, opposition) of their children. Ratings of mothers of children with ADHD were compared to mothers of children without ADHD. Moreover, as medication was administered once per day and the assessments were conducted twice per day, duration of the medication effect could be established.

So far, studies have shown that ESM/EMA can be applied (1) to monitor the immediate effects of ADHD medications in daily life, (2) to reveal situation-specificity in the effects of ADHD medication, (3) to distinguish between medicated children with ADHD and healthy controls, and (4) to provide insight into duration of effect of medication.

### 3.4. Schizophrenia and other psychotic disorders

Two studies have examined the effects of medication on emotional experience in patients with a psychotic disorder ([Lataster et al., 2011b, 2011a](#)). [Lataster et al. \(2011b\)](#) compared haloperidol and risperidone, considered tight-binding

agents to the dopamine D<sub>2</sub> receptor, to olanzapine, a loose-binding agent. ESM/EMA was used to assess psychotic symptoms, mood, context, and appraisals of the current situation. The authors examined whether and how the relationship between dose and emotional experience and symptoms differed for tight- and loose-binding agents.

In another study, [Lataster et al. \(2011a\)](#) examined emotional responses to switching from a traditional dopamine antagonist (olanzapine, pimozide, haloperidol, or quetiapine) to a partial dopamine agonist (aripiprazole). ESM/EMA was conducted at baseline when patients were still taking the traditional medication and again after five weeks of aripiprazole. The authors examined how mood and psychotic symptoms changed as a result of switching the medication.

In sum, ESM/EMA has been used in patients with a psychotic disorder to increase insight into the working mechanisms of medication with respect to emotional experience and symptoms in daily life.

### 3.5. Anxiety disorders

To date, there has been one ESM/EMA study on the pharmacological treatment of anxiety disorders in adults [Sheehan et al. \(2007\)](#) and one in youth [Forbes et al. \(2012\)](#).

In adults with panic disorder, [Sheehan et al. \(2007\)](#) compared the extended release (XR) formulation of alprazolam to the compressed tablet (CT) formulation. Patients were prescribed alprazolam-CT for three weeks and were then switched to six weeks of alprazolam-XR. For the entire treatment period, patients indicated every waking hour how much anxiety relief they experienced from the medication. The study examined the rate at which peak benefit was obtained as well as the duration of effectiveness.

[Forbes et al. \(2012\)](#) studied the effects of pharmacological treatment on the affective and social dynamics of youth with an anxiety disorder and/or MDD. Participants could choose among a selective serotonin reuptake inhibitor, cognitive-behavioral therapy, or a combination. Before, during, and immediately after treatment, ESM/EMA was used to monitor mood, current activities, and the presence of others, during five weekends (Friday-Monday). Baseline ESM/EMA variables such as negative affect, positive affect, and social time expenditure (e.g., amount of time spent with parents versus peers) were used as predictors of changes during treatment and outcomes after treatment. Importantly, baseline momentary affect offered information on treatment response and course above and beyond the traditional baseline questionnaires.

In sum, studies on the psychopharmacology of anxiety disorders have shown that ESM/EMA can be applied (1) to study the effect duration of medication, (2) to study the role of social time expenditure on treatment course and response, and (3) to predict the response to and course of treatment by assessing the dynamics of mood before and during treatment. This yields additional information over and beyond traditional measures.

## 4. Discussion

ESM/EMA has been applied to study pharmacological interventions for MDD, substance use disorders, ADHD, psychotic

disorders, and anxiety disorders. Here we consider those applications that are particularly relevant to psychopharmacology. We also mention directions worth pursuing in future research and we touch upon the potential of ESM/EMA to be integrated into clinical practice.

### 4.1. Applications of ESM/EMA for psychopharmacology

Our review shows that ESM/EMA might help characterize patients before, during, and after pharmacological treatment ([Fig. 1](#)). Before treatment, baseline affective characteristics assessed using ESM/EMA were found to predict treatment outcomes ([Höhn et al., 2013](#); [Peeters et al., 2010](#); [Wichers et al. \(2012\)](#); [Forbes et al. 2012](#)). This has mainly been studied in patients with MDD. For example, [Höhn et al. \(2013\)](#) found that the ability to savor positive affect for longer periods of time was associated with better treatment response.

During treatment, ESM/EMA has been used to examine subtle changes in affect and side effects in the first week of treatment as a predictor of later response and remission ([Geschwind et al., 2011](#); [Barge-Schaapveld and Nicolson, 2002](#)). Further, ESM/EMA might be used to identify predictors of and protectors against relapse in the patients' natural environments ([Holt et al., 2012](#)). This opens the possibility for clinicians to offer patients additional guidance in high-risk situations during treatment. Furthermore, ESM/EMA during treatment might offer psychopharmacologists better insight into when doses wear off. For example, using ESM/EMA, [Sheehan et al. \(2007\)](#) were able to show that extended-release alprazolam is longer-lasting in anxiety disorder patients than the compressed-tablet formulation. Similarly, ESM/EMA data have revealed that atomoxetine may have a more enduring effect in children with ADHD than stimulants ([Whalen et al. 2010](#)).

Another potential advantage of applying ESM/EMA during treatment may be its sensitivity to context-specific treatment effects. For example, using ESM/EMA, [Gehricke et al. \(2011\)](#) were able to reveal that ADHD medication may specifically reduce concentration problems during stressful situations and smoking abstinence. Similarly, using ESM/EMA, [Whalen et al. \(2010\)](#) showed that atomoxetine was more effective than stimulants in reducing ADHD symptoms in the morning (but not in the evening). This suggests that ESM/EMA can be used to illuminate the effects of medication in different situations and at different time points, which might ultimately help inform clinicians in which contexts additional help is needed.

Finally, after treatment, ESM/EMA might illuminate the effects of medication on several aspects of daily life, for example on symptoms ([Lataster et al., 2011a](#)), positive and negative affect ([Wichers et al., 2009](#)), quality of life ([Barge-Schaapveld and Nicolson, 2002](#)), the amount of time spent on daily activities ([Barge-Schaapveld et al., 1995](#)), and the number of drinks consumed ([Tidey et al., 2008](#)). Moreover, ESM/EMA has been shown to help detect differences between healthy individuals and patients in remission even when traditional clinical predictors indicate normalization ([Barge-Schaapveld and Nicolson, 2002](#); [Whalen et al. 2010](#)) and identify predictors of relapse after treatment termination in the patients' natural environments ([Cooney et al.,](#)



2007). For patients receiving long-term treatment, ESM/EMA may help identify vulnerabilities that might need additional attention. For example, medicated children with ADHD continue to show more negative affect and behavioral symptoms than healthy controls, even after having been successfully medicated for at least two months (Whalen et al. 2010).

Across treatment phases, ESM/EMA measures have shown predictive value above and beyond traditional measures (Geschwind et al., 2011; Forbes et al. 2012; Peeters et al., 2010). Peeters et al. (2010) found that emotional reactivity predicted depression severity after one month of treatment over and above traditional clinical predictors, such as baseline depression severity, episode duration, and mean levels of reported mood. Also, adding early changes in positive affect to a model already containing early changes in HDRS scores significantly improved the accuracy of the prediction of depressive symptoms, response to treatment, and remission after six weeks of treatment (Geschwind et al., 2011). Lastly, Forbes et al. (2012) found that ESM/EMA-derived affect was predictive of the rate of change in symptoms over the course of treatment, whereas traditional self-report assessments of depressive and anxiety symptoms were not.

#### 4.2. Limitations of this review

With this review, we aimed to give an overview of the use of ESM/EMA in examining the pharmacological treatment for all DSM-IV disorders. However, there are some limitations.

First, we did not include daily diary studies. In these studies, assessments are conducted only once per day, which is fundamentally different from ESM/EMA in that daily diaries cannot be used to examine within-day fluctuations in symptoms and mood. Further, daily diaries require participants to reflect on a day at the end of that day, rather than report about their current state, which might yield biased results (Myin-Germeys, 2012). Furthermore, unlike ESM/EMA studies, daily diary studies cannot offer insight into the context-specificity of medication effects and the immediate precipitants of drinking and smoking. In spite of these limitations, however, since daily diaries are less time-consuming and burdening for participants and researchers, they may still be used instead of ESM/EMA. For example, Lenderking et al. (2008) found that diaries completed at the end of the day detected antidepressant onset and response more quickly than standard weekly assessments.

Second, our findings are based on a limited number of ESM/EMA studies, some of which were conducted in the same data sets. As pointed out by an anonymous reviewer, due to the variation in the terminology that has been used to describe ESM/EMA, we might have overlooked some eligible studies. Nevertheless, these numbers in the field of psychopharmacology are likely very low, considering the growing popularity of ESM/EMA in the fields of psychiatry, clinical psychology, and biopsychology. We encourage replication of the present findings so conclusions about the usefulness of ESM/EMA can be more powerfully drawn. Moreover, as most ESM/EMA pharmacology studies were

conducted in patients with MDD, they should be extended to studies conducted in other clinical populations.

#### 4.3. Limitations of ESM/EMA

Before discussing how ESM/EMA may be used in future human psychopharmacological studies, we wish to point out that we believe these studies are very feasible. It has been argued that ESM/EMA may be too demanding for patients with severe mental illness, who are particularly likely to receive pharmacological treatment, resulting in a selection bias. Nevertheless, compliance levels were acceptable in patients with psychiatric disorders who did participate in ESM/EMA studies (Hufford and Shields, 2002). Some studies did not report any data on compliance, which limits our understanding of the reliability and validity of the conclusions that may be drawn. However, most other studies reported adequate compliance (Table 1). One study did report a high dropout rate, but this was unrelated to the inability to comply with the ESM/EMA protocol (Lataster et al., 2011a). Overall, we believe it is feasible to include ESM/EMA in psychopharmacology research and practice. The study length and data sampling rate can be adjusted to the specific questions and the patients under study.

While we do not have any reservations with respect to feasibility, we do have some reservations about the validity of the ESM/EMA questionnaire items used to date. Past ESM/EMA studies have often adapted items from retrospective questionnaires. For example, questions about mood tend to be derived from the Positive and Negative Affect Scale (PANAS; Watson et al., 1988). One problem could be that the meaning of a certain item changes over the course of treatment for a given patient, a phenomenon known as response shift (Barclay-Goddard et al., 2009). For example, at the end of the treatment patients might feel as sad as at the beginning of the treatment, but more able to cope with it. If they would score the same ESM/EMA questionnaire item differently while they are feeling the same, then this would limit insight into the processes of change that occurred during treatment. Future research should determine the degree of response shift that might occur in ESM/EMA questionnaires applied to clinical psychopharmacology research.

Previous ESM/EMA research often took a paper-and-pencil approach to data collection, which precludes insight into whether patients actually complete the questionnaires as instructed. It has been suggested that compliance with paper-and-pencil ESM/EMA approaches is poor: patients may complete questionnaires with a significant delay or complete all delayed questionnaires at once, which retains memory biases Stone et al. (2002). These issues can be solved with electronic devices such as PDAs and mobile phones, which time-stamp entries and limit access to the questions to certain time intervals. Electronic data collection is thought to yield data that are as valid as those obtained using paper-and-pencil approaches (Gwaltney et al., 2008). Thus, collecting data electronically seems to have definite benefits. ESM/EMA software and technology that lessen the burden of data collection to the researcher have become increasingly available (Intille, 2012).

Interestingly, in spite of the growing interest to use ESM/EMA in pharmacological research, the Food and Drug

Administration (FDA) guidelines on Patient-Reported Outcome Measures offer little guidance on how to properly conduct ESM/EMA in pharmacological research (Food and Drug Administration, 2009). We believe clear guidelines are necessary to help researchers determine the appropriate methodological details and derive valid conclusions from the data.

#### 4.4. Future directions

Studies on MDD indicate that ESM/EMA may be used to monitor patients at different phases of treatment, that this monitoring can help predict clinical outcomes, and that ESM/EMA may show superiority over traditional measures in identifying individuals at risk for relapse (Barge-Schaapveld and Nicolson, 2002; Geschwind et al., 2011; Höhn et al., 2013; Peeters et al., 2010; Wichers et al., 2009, 2012). ESM/EMA may be used for similar purposes in patients with diagnoses other than the ones studied to date.

Two studies found that ESM/EMA was able to reveal the effectiveness of medications in different situations (Whalen et al., 2006; Gehricke et al., 2011). This context-sensitivity of ESM/EMA is highly relevant to psychopharmacology. For example, in future research, ESM/EMA might also be used to investigate the extent to which ADHD medication has different effects at home and at school.

In two other studies, ESM/EMA helped reveal the duration of the effects of psychotropic medication (Whalen et al., 2010; Sheehan et al., 2007). This opens up exciting possibilities of adjusting treatment to accommodate individual differences in treatment response due to varying metabolic rates, for example. Patients may then be able to benefit from treatment more optimally. Relatedly, as ESM/EMA involves the sampling of data at short intervals, it could help chart the effects of rapid-acting compounds with short-lasting effects such as ketamine for MDD (aan het Rot et al., 2012b). Adding ESM/EMA to studies on experimental therapeutics might generate valuable novel insights.

ESM/EMA studies often yield many observations per participant and thus allow for the study of within-person processes, which is difficult to impossible with traditional retrospective measures (Hamaker, 2012). Studies comparing groups assume that findings at the population level are generalizable to the individual, but this assumption is almost never appropriate when studying dynamic processes that change over time (Molenaar, 2004). Consequently, the within-person approach is increasingly recognized as an important addition to the traditional between-groups approach (Hamaker, 2012). This is highly relevant for psychopharmacology as it might lead to more person-tailored interventions. Moreover, adding ESM/EMA to psychopharmacology studies might generate new insights into the causal mechanisms underlying the effects of treatment on specific symptoms of a mental disorder. For example, Young et al. (2014) argued that antidepressants might partially work by altering how depressed patients interact with others and that this could be studied using ESM/EMA.

Lastly, we encourage psychopharmacologists to consider how ESM/EMA could be applied to study the effects of medications on aspects of daily life other than affect and symptoms, which have been the focus to date. Social

interactions constitute one relevant example, since they form a large part of daily experience and are often altered in individuals with psychiatric diagnoses (e.g., Brown et al., 2011; Kashdan and Farmer, 2014). ESM/EMA has already been used to examine the effect of tryptophan on social interactions in a non-clinical population reporting interpersonal problems (aan het Rot et al., 2006). Yet other aspects of life can be studied using ambulatory devices and even personal smartphone applications that measure e.g. physical activity, light exposure, sleep, and aspects of cardiovascular function (Bruining et al., 2014), variables that may also be relevant to the field of psychopharmacology. For example, sleep disturbances occur in many mental disorders.

#### 4.5. Clinical implications

ESM/EMA may become an effective tool in clinical practice (Wichers et al., 2011b): ecological momentary interventions (EMI) can be integrated with pharmacological treatment to provide both psychopharmacologists and patients with person-tailored feedback on progress (EMI, Heron and Smyth, 2010). As EMI teaches patients how their responses to their usual environments change in the context of pharmacological treatment, it can bring about long-lasting psychological changes. Interestingly, the detailed feedback that ESM/EMA provides may stimulate shared decision making by patients and their clinicians (Wichers et al., 2011a). Kramer et al. (2014) recently investigated the effectiveness of adding EMI to pharmacological treatment. Results indicated that this was clinically more effective in reducing depressive symptoms than pharmacological treatment alone, and than pharmacological treatment plus ESM/EMA without person-tailored feedback.

### 5. Conclusion

We have shown how ESM/EMA has been used in psychopharmacology research to date. We have described how ESM/EMA can be applied in multiple phases of treatment to examine what happens at the micro-level and to predict future outcomes. It is becoming increasingly clear that ESM/EMA can provide unique insights in how daily life experiences might change as a result of treatment. With this in mind, researchers and clinicians may have obtained a powerful tool that can help optimize the care of individuals diagnosed with mental illness.

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#### Author contributions

F.M. Bos drafted the article and M. aan het Rot and R.A. Schoevers revised it critically and offered important input. All authors contributed substantially to the conception and design of this manuscript and gave final approval of this version to be published.

## Conflict of interest

All authors state that they have no conflicts of interest.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.euroneuro.2015.08.008>.

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