

A Systematic Review of Studies Comparing Actigraphy Indices in Patients with Depression and Schizophrenia

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ABSTRACT

Introduction: Abnormalities in sleep-wake activities are frequently observed among patients with depression and schizophrenia. These abnormalities are variable and may have discriminative, clinical, diagnostic, and therapeutic significance if measured objectively with actigraphy.

Aim: To systematically review the published literature on actigraphy in depression and schizophrenia, particularly to identify areas of research that need to be addressed before their clinical application in practice.

Materials and Methods: The electronic databases (PubMed and Google Scholar) were searched for studies using the key terms 'actigraphy' OR 'actigraphic recording' OR 'wrist actigraphy' OR 'actometer' OR 'actimeter' OR 'actical' OR 'actiwatch' OR 'sleep-watch' AND 'schizoaffective' OR 'schizophr*' OR 'psychosis' AND 'depression' OR 'depressive' in title and abstract. The literature search was limited to articles published in English and until 31st December, 2020. Data were abstracted by two reviewers and presented as a narrative summary of the findings. A qualitative synthesis of the study designs, populations, and outcomes was

conducted. The quantitative synthesis of the results was not possible to conduct due to the heterogeneity and scarcity of the included studies.

Results: Out of 33 searched articles, a total of four studies (three observational and one case report) were included for the review. The included studies were heterogeneous, small in sample size, divergent in methods, inclusive of clinical population, having more than two groups (depression, schizophrenia, mania, or bipolar disorders), and with a low degree of evidence. Overall, the patients with schizophrenia have more structured and less complex activity pattern than those with depression. Furthermore, the patients with schizophrenia showed more irregular patterns in the morning period and increased fluctuations inactivity in the evening period than depression patients.

Conclusion: Currently, available information is insufficient to draw firm conclusions on use of actigraphy indices (e.g., duration of active periods, a pattern of activity, and sleep) for diagnosis and discrimination among the patients with schizophrenia and depression. Large, prospective, and comparative studies are required to identify role of actigraphy among these patients.

Keywords: Accelerometry, Mental health, Psychosis, Sleep

INTRODUCTION

The altered sleep-activity levels (i.e., psychomotor retardation or agitation) is one the recognised feature of both depression and schizophrenia [1-4]. Nonetheless, these symptoms are frequently reported in patients with depression and are one of the diagnostic criteria for Major Depressive Disorder (MDD) [4]. These symptoms are indicative of a complex underlying neurobiological mechanism such as diurnal variation in cortisol or depression, neurotransmitters, illness process, and effects of medications (e.g., extrapyramidal effects of antipsychotics) [5,6].

Sleep and psychomotor activity are also a predictor of clinical response and remission in symptoms of schizophrenia and depression [7]. These two disorders differ from normal, other psychiatric conditions, and from each other in terms of gross motor activity, body movement, reaction time, and speech [8]. However, the clinical evaluation and monitoring of these symptoms are challenging due to subjective scales and measures [9,10].

On other hand, body worn accelerometers (actigraphy) can be used to monitor the sleep-activity. Monitoring of these sleep-activity patterns using actigraphy has been found useful in patients with schizophrenia, depression, and psychosis [11-13]. The actigraphic motor activity pattern differs among the patients with schizophrenia and depression [14]. The actigraphy can be used as an objective clinical measure of psychomotor activities and to track the progression of mood disorders [15,16]. Thus, actigraphy could be a promising discriminative marker in clinical practice for these two groups of patients. Furthermore, the putative value of actigraphy may lie in the ability to identify subgroups (e.g., low/high sleep-activity), monitor dimensions (e.g., negative

symptoms or motor behaviour), and outcome marker of symptoms (e.g., avolition, quality of life) [17-19].

However, there was no systematic review that attempted to compare actigraphy indices in patients with depression and schizophrenia. This systematic review was conducted to examine published studies in which actigraphy was used to compare the sleep-activity pattern between these two groups in order to identify areas of research that need to be addressed before their clinical application in practice.

MATERIALS AND METHODS

In December 2020-January 2021, this systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [20].

Inclusion criteria: Studies fulfilling the following criteria were considered eligible for inclusion in the study:

1. Population: Patients with schizophrenia and depression regardless of any subtype of illness, age, gender, medications status (naïve, on treatment), treatment setting (inpatients or outpatients), or other clinical characteristics.
2. Investigation: Actigraphy measurement.
3. Comparison: Studies having at least these two groups (patients with schizophrenia compared with patients with depression).
4. Outcomes: Actigraphy-related outcomes (actigraphy), remission in clinical symptoms.
5. Study design: Descriptive (case report or case series) and analytical studies (cross-sectional, case-control, or cohort).

Exclusion criteria: Studies assessing other conditions (e.g., obesity, sleep disorders, cancer, diabetes, or parkinsons disease), lacking the comparison between depression and schizophrenia, and studies that include reviews, protocol, or correspondences, and published in a language other than English were excluded.

Search strategy: PubMed and Google Scholar databases were searched till 31st December, 2020. The literature search was carried out using the three groups of terms 'actigraphy' OR 'actigraphic recording' OR 'wrist actigraphy' OR 'actometer' OR 'actimeter' OR 'actical' OR 'actiwatch' OR 'sleep-watch' AND 'schizoffective' OR 'schizophr*' OR 'psychosis' AND 'depression' OR 'depressive' and was limited to title and abstract. The filters were restricted to studies available in the English language. The reference lists of the final included studies were also hand-searched and Google Scholar was used to find articles that cited these studies.

Selection Process

Zotero[®] software was used to import all studies obtained from the literature search. After the removal of duplicates, the two authors (RR and AK) reviewed the title and abstract independently and then jointly to identify the potentially eligible studies based on inclusion and exclusion criteria. At the screening stage, any disagreement was resolved by including the article in the full text. Then the full text screenings of articles were done by two authors (RR and AM). The disagreement if any was resolved by consensus and a discussion with the fourth author (PP).

Data Abstraction and Risk of Bias Assessment

Two authors (RR and AM) independently extracted the data of interest from the full texts of the eligible studies. The data comprised the following information: study design, year of the study, sample characteristics, actigraphic parameters (e.g., duration of monitoring, duration of activities), relevant outcomes, potential confounders, and conflict of interest. Any discrepancies were corrected by referring to original studies and resolved by consensus. Two reviewers (RR and AM) independently assessed the risk of bias based on GRADE 4 guidelines in each eligible study [21]. The disagreement if any was resolved by consensus and a discussion with the fourth author (PP).

STATISTICAL ANALYSIS

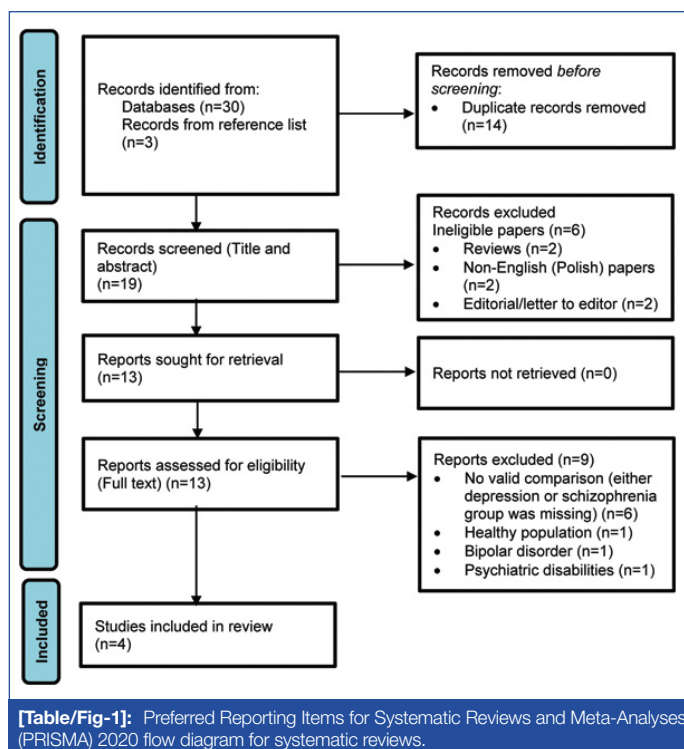
A qualitative synthesis of the study designs, populations, and outcomes was conducted. The quantitative synthesis of the results was not possible to conduct due to the heterogeneity and scarcity of the included studies.

RESULTS

A total of 30 potentially eligible studies were obtained after the electronic search of the two databases. Additionally, three records were found in the reference list of identified studies. After the removal of duplicates, a total of 19 records were processed via title and abstract screening. Among the 13 studies, which were full text screened, another nine studies were excluded. Finally, four articles were selected for qualitative analysis [Table/Fig-1].

Study characteristics and risk of bias: Of the included studies, three were observational longitudinal studies [14,22,23], while one was a case report [Table/Fig-2] [24]. These studies were carried out on the clinical population receiving in-patient treatment. Interventional studies were not found in a literature review. The studies were conducted in Norway (n=3) and Switzerland (n=1). Based on GRADE 4 guidelines, there was a considerable bias of moderate risk in the methodological quality of these non randomised observational studies [21].

Synthesis of results: More than two groups (schizophrenia, mania, depression, and healthy controls) were compared for actigraphy recordings for the duration of 12 days to 14 days [14,22,23]. In



observational studies, the participants receiving medications such as antipsychotics or other drugs were included. However, these participants were not matched for age, gender, and socio-demographic factors.

Study tools/scales: Berle JO et al., and Fasmer OB et al., used the semi-structured interview SCID-I along with Montgomery-Asberg Depression Rating Scale (MADRS) and Brief Psychiatric Rating Scale (BPRS) to rate the symptoms of depression and schizophrenia in their study [14,23]. On other hand, Krane-Gartiser K et al., used ICD-10 research diagnostic criteria without any additional rating scales for the diagnostic evaluation [22]. In a case study, Haug HJ et al., did not employ a scale or mention diagnostic criteria for evaluating patients [24].

Concurrent medications: The effects of these medications on actigraphy parameters were not studied in other reported studies except Berle JO et al., and Krane-Gartiser K et al., [14,22]. Berle JO et al., compared the patients with schizophrenia who were treated with clozapine with those treated with other antipsychotics [14]. In Krane-Gartiser K et al., study the patients with schizophrenia were treated most commonly by antipsychotics with or without hypnotics or sedatives or mood stabilisers, while those with depression were treated by using antidepressants with or without hypnotics or mood stabilisers [22] [Table/Fig-1].

Actigraphy indices: The actigraphy was placed on the non dominant hand [24], while in some studies it was placed on hand as per patient convenience [14,23]. Variable actigraphy devices and measurement protocols were used by authors. Berle JO et al., used actigraphy indices such as gross motor activity, interdaily stability, intradaily variability, and relative amplitude [14]. Fasmer OB et al., has evaluated the mean activity scores, active and inactive period [23].

Actigraphy outcome: Berle JO et al., found that patients with schizophrenia had a more pronounced reduction in night time activity and lower intradaily variability than patients with depression [14]. Intradaily stability was a little higher in patients with schizophrenia than in patients with depression. They didn't found any significant correlation between either MADRS or BPRS with different actigraphy motor parameters.

Fasmer OB et al., found no significant difference between the schizophrenia and depression groups in the mean length of the longest active period [23]. The schizophrenia group had a higher mean value for an inactive period duration and a higher percentage of inactive periods (Duration: ≥ 21 minutes) compared to the depression

| Author (year) | Sample characteristics | Assessment tools | Actigraphy device/ Placement | Actigraphic parameters | Concurrent medications | Key findings | Comments |
|--------------------------------------|---|-------------------------------------|---|--|--|---|--|
| Krane-Gartiser K et al., (2018) [22] | Schizophrenia (n=28), Mania(n=18), Unipolar depression (n=25) and Non-hospitalised healthy individuals (n=28) | ICD-10 research diagnostic criteria | Philips Respironics Inc., Murrysville PA, USA | 24 hours wrist actigraphy Mean activity count/ minute 64-min periods (sample entropy, autocorrelation) | Schizophrenia: Antipsychotics (n=20), Hypnotics/anxiolytics (n=10), Anticonvulsants (n=4), Antidepressants(n=3), Antihistamines (n=2), No psychotropic drug treatment (n=5) Depression: Antipsychotics (n=6), Hypnotics/anxiolytics (n=12), Anticonvulsants (n=3), Antidepressants (n=9), Antihistamines (n=2), ECT (n=1), No psychotropic drug treatment (n=5) | Irregular activity patterns: Schizophrenia >depression Mean level of activity: depression<schizophrenia. | Hospitalised patients were compared with non-hospitalised healthy controls |
| Fasmer OB et al., (2016) [23] | Schizophrenia (n=24), depression (n=23) and healthy controls (n=29) 12 days of actigraphy recording | SCID-I, MADRS, BPRS | Cambridge Neurotechnology Ltd /Right hand (Patient convenience) | Wrist actigraphy for at least 12 days Active and inactive periods | Schizophrenia: Antipsychotics: clozapine (n=9), second generation (n=8), traditional (n=6), a combination of traditional and second generation drugs (n=2). Depression: No medications (n=8), one antidepressant (n=13), two antidepressants (n=2), lithium (n=5), valproate (n=1), antipsychotics (n=5, low dose), Hypnotics / benzodiazepine (n=3). | Mean duration of active periods: depression < schizophrenia Duration of inactive periods: schizophrenia>depression | Treatment with psychotropic, age, and gender were confounding factors. No separate analysis of sleep parameters |
| Berle JO et al., (2010) [14] | Schizophrenia (n=23), Depression (n=23, 5 inpatients), Healthy controls (n=23, Hospital employees) | SCID-I, MADRS, BPRS. | Cambridge Neurotechnology Ltd./Right hand (Patient convenience) | Wrist actigraphy for 2 weeks Gross motor activity, Interdaily stability, Intradaily variability, Relative amplitude | Schizophrenia: clozapine and other antipsychotics MDD: antidepressants, some co-medicated with lithium, mood stabilisers, antipsychotics, anxiolytics or hypnotics, | Total activity, Activity night, Intradaily variability, and Relative amplitude: Depression> schizophrenia Interdaily stability: Depression < schizophrenia | Small sample size, no systematic assessment of adverse events (e.g., the side-effect of motoric type) |
| Haug HJ, et al., (2000) [24] | Schizophrenia (n=1, 42 years, male): inpatient Depression with OCD (n=1, 33 years, female) | No scale or any diagnostic criteria | Cambridge Neurotechnology Ltd./Non-dominant hand (left) | 24 hours wrist actigraphy for 2 weeks. | Schizophrenia: Clozapine, Clonazepam. Depression: Olanzapine, Venlafaxine | Depression: Very regular rest-activity rhythm Schizophrenia: Very low morning activity | Depression with OCD, case comparison |

[Table/Fig-2]: Summary of studies comparing the actigraphy indices in patients with depression and schizophrenia [14,22,23,24].

MADRS: Montgomery-asberg depression rating scale, BPRS: Brief psychiatric rating scale, MDD: major depressive disorder, OCD: obsessive-compulsive disorder, SCID-I: Structured clinical interview for DSM-IV axis I disorders

group. While the depression group has a lower percentage of active periods (Duration: ≥ 36 min) compared to the schizophrenia group. Krane-Gartiser K et al., demonstrated that the depression group has the lowest mean level of activity than the schizophrenia group. Also, the depression group displayed increased fluctuations from the mean, successive count variability, and more shifts between inactivity and activity [22]. The cases with schizophrenia showed more irregular patterns in the morning period and increased fluctuations inactivity in the evening period than depression cases [22]. However, no significant difference was observed in mean activity over 24 hours after adjusting the medication treatment [22].

DISCUSSION

Though the published studies attempted to understand the role of sleep-activity pattern, motor activities, none attempted to compare the clinical parameters (e.g., total sleep time, total night-time sleep, total wake time, wake after sleep onset, total awakenings, sleep latency, sleep efficiency). These parameters can have a vital role in the diagnosis and management of these conditions. Also, there was variation in actigraphy placement, previous studies have shown small differences between the right and left wrist [25,26].

The pattern of motor activity among patients with schizophrenia was less complex than patients with depression [14]. Further, the patients treated with clozapine had a more pronounced reduction in night time activity, increased interdaily stability, and reduced intradaily variability than the non-clozapine group [14]. The actigraphy parameters such as sleep efficiency, sleep continuity, sleep latency, and variability in sleep hours in patients with schizophrenia could be valuable in measuring the effect of antipsychotic or antidepressant [27]. Circadian disruption is associated with a high risk for schizophrenia and depression and associated with increased serum cortisol and

inflammatory activity [28,29]. But, the lack of studies about this topic restricts the understanding of the relationship between these indices and complex psychopathology linked with worse prognosis, as the severity, treatment response, and non-remission. In addition, age and gender affect the actigraphy indices; the lack of matched controls in most of the studies affects the clinical utility of these findings [23].

These four studies have used a wide range of assessment protocols (e.g., total motor activity, intradaily activities), and were mainly confined to hospital inpatients. Certain clinical parameters such as Body Mass Index (BMI), socio-demographic characteristics, co-morbidities (e.g., substance use, diabetes) were not compared in these studies. The activity level as measured by actigraphy is often indicative of the severity and course of negative symptoms, as well as lifestyle choices and nosological entities among these patients [18]. Therefore, population-based, clinical, interventional, and longitudinal studies are required to predict their role in remission and relapse in subsequent studies.

The poor sleep quality, altered sleep duration, number of awakenings has been associated with residual mood symptoms or psychotic symptoms and as an independent risk factor for these conditions due to the possible involvement of serotonergic pathways [30-32]. This finding enforces the importance of investigating the role of actigraphy indices to elucidate the underlying pathophysiological mechanisms.

This review is the first to provide analyses of published studies that attempted to compare the actigraphy pattern among patients with schizophrenia and depression. The evidence clarifies some issues and gives direction for further research. We have not registered our review protocol with Prospero and this review is part of our ongoing study [33].

Limitation(s)

The limited sample size and small number of studies limit the generalisation of study findings for clinical use. Also, the lack of comparative subjective clinical scales (e.g., Pittsburgh sleep quality index, insomnia severity index), gold standard methods (e.g., polysomnography), and biomarkers (e.g., sleep electroencephalogram, hormones: cortisol, melatonin, or other hormones) in these studies limits the clinical utilisation of actigraphy in clinical practice. The small number of studies, heterogeneity of study designs, study tools/instruments, and study population prevented us from performing meta-analysis. These studies were observational and findings were also confounded by concurrent administration of medications.

CONCLUSION(S)

In terms of sleep motor activity, actigraphy reveals that people with schizophrenia differ from those with depression. However, clinical and pathophysiological importance of these motor activity complexities in these patients was inconclusive. The study findings though promising require further evaluation with polysomnography, subjective measures of sleep, and biomarkers. Also, studies should focus on the diagnostic, prognostic, and clinical significance of actigraphy in these groups of patients.

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