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Pathogenesis and management of Brugada syndrome in schizophrenia: A scoping review

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ABSTRACT

Context: Excess cardiovascular morbidity and an increased prevalence of sudden cardiac death (SCD) contributes to premature mortality in schizophrenia. Brugada syndrome (BrS) is an important but underrecognized cause of SCD. It is more commonly seen in schizophrenia than in general population controls.

Methods: We conducted a scoping review to describe the pathogenesis of BrS in schizophrenia and to identify the psychotropic medications that increase the risk of unmasking BrS and associated ventricular arrhythmias resulting in SCD.

Findings: Schizophrenia and BrS share similar calcium channel abnormalities, which may result in aberrant myocardial conductivity. It remains uncertain if there is a genetic pre-disposition for BrS in a subset of patients with schizophrenia. However, the unmasking of Brugada ECG patterns with the use of certain antipsychotics and antidepressants increases the risk of precipitating SCD, independent of QT prolongation.

Conclusions and future directions: Specific cardiology assessment and interventions may be required for the congenital or unmasked Brugada ECG pattern in schizophrenia. The current long-term standard of care for BrS is an implantable cardioverter defibrillator (ICD), but post-implantation psychological effects must be considered. Careful use of antipsychotic and other psychotropic medications is necessary to minimize proarrhythmic effects due to impact on cardiac sodium and calcium ion channels. When prescribing such drugs to patients with schizophrenia, clinicians should be mindful of the potentially fatal unmasking of Brugada ECG patterns and how to manage it. We present recommendations for psychiatrists managing this patient population.

1. Introduction: background and terminology

Cardiovascular disease (CVD) contributes significantly to the morbidity and mortality of patients with schizophrenia [1]. The mortality gap due to CVD in patients with schizophrenia and the general population is increasing over time [1,2]. Indeed, the mean age of CVD-related mortality is approximately 10 years younger in people with schizophrenia compared to the general population [3]. Several large-scale cohort studies have estimated that nearly 40% of patients with schizophrenia die from cardiovascular complications including coronary artery disease, myocardial infarction, myocarditis, and sudden cardiac death (SCD) [2–5]. SCD has been comparatively understudied, yet represents 15–40% of all sudden unexplained deaths in people with schizophrenia [6], with some studies estimating threefold higher when compared to the general public [4].

The cause of SCD is often difficult to elucidate due to its multifactorial etiology. SCD is generally defined as an unexpected death within one hour of the onset of symptoms, usually due to a malignant cardiac arrhythmia [7]. Suggested underlying factors for SCD in schizophrenia include ischemic heart disease and QT prolongation due to antipsychotic drugs [8,9], decreased heart rate variability and autonomic dysfunction [10], and Brugada Syndrome (BrS) or inducible...
Brugada ECG patterns [11–13].

BrS represents up to 20% of SCD in people with structurally normal hearts with a prevalence ranging from 1 in 5000 to 1 in 2000 [14]. It is more common in males [14]. Apart from SCD being a possible outcome of BrS, clinical manifestations include atrial fibrillation, arrivoventricular block, and syncope [14].

The diagnosis of BrS is made by ECG showing a coved ST segment elevation of ≥2 mm in one or more of V1 and V2 in the second, third, or fourth intercostal space according to 2015 European Society of Cardiology guidelines [15]. This is known as type 1 morphology and is diagnostic of BrS. A type 2 morphology also exists (saddleback ST elevations ≥1 mm), which, while raising suspicion for BrS, is not diagnostic [16]. A type 3 morphology has also been described with ST segment elevations; coved or saddleback, ≤ 1 mm [17]. Patients with type 2 or type 3 morphologies are diagnosed with BrS when a sodium channel blocker challenge, or an inducing factor such as fever or medications, converts their ECG to a type 1 morphology [18].

A novel diagnostic tool, the Shanghai Score System for BrS, has been proposed [18]. This combines ECG findings (spontaneous type 1, fever-induced type 1 and type 2 or 3 conversion to type 1), clinical history, and family history into a score that falls into one of three categories: 1) Probable / definite BrS, 2) Possible BrS, 3) Non-diagnostic. This scoring system requires ongoing validation until international consensus is reached.

The terminology surrounding BrS can be confusing. There are two separate disorders that can manifest with a type 1 ECG morphology. BrS is considered a true congenital disorder that leads to a type 1 ECG morphology. Patients with normal baseline ECG findings can have BrS unmasked by a variety of triggers including fever, metabolic disorders, and pharmacological therapies such as sodium channel blockers [19].

The Brugada phenotype (BrP) shares the same risk factors as BrS. It can also be induced by reversible conditions including adrenal insufficiency, hypokalemia, or myocardial ischemia that induce a type 1 morphology, which resolves once the underlying cause is corrected [19]. This is an important delineation: BrP can resolve from the removal of inducing factors, but BrS persists as an underlying channelopathy despite removal of such factors. Other key features of BrP include the absence of family history of SCD, no seizures, syncope or nocturnal agonal respiration, and a negative challenge test with sodium channel blockers like ajmaline [19]. A sodium channel blocker cannot unmask BrS but not necessarily BrP, however its utility in screening has not been established. This difference in terminology is important, as patients with BrS may benefit from implanted cardioverter-defibrillators (ICD), while BrP treatment recommendations focus on treating the underlying cause that unmasks the ECG pattern.

Despite BrS being a known cause of SCD in the general population, little is known about its contribution to SCD in SCZ. One reason may be the ambiguous terminology surrounding “Brugada Syndrome”, “Brugada Phenotype” (BrP), “unmasked Brugada”, and “Brugada ECG patterns”. Nonetheless, emerging evidence of Brugada ECG patterns in patients with schizophrenia and those taking antipsychotic medications warrants closer investigation. Given that the existing literature on Brugada syndrome in schizophrenia is sparse, and non-systematised, we conducted a scoping review. The aim of this scoping review was to perform a comprehensive overview of studies describing the epidemiology of BrS and Brugada ECG pattern in schizophrenia, possible pathophysiological mechanisms shared between schizophrenia and BrS as well as the use of antipsychotic and other psychotropic medications which may predispose people with schizophrenia to developing Brugada ECG patterns and related SCD.

2. Methods

This scoping review was based on the methodology outlined by Arksey and O’Malley [20]. A scoping review was conducted on studies of BrS in schizophrenia to provide evidence-based information on definition, epidemiology, risk factors, clinical features and management.

A scoping review allows us to appraise, synthesise and disseminate research findings on a condition that is relatively understudied in psychiatric research. The topic of BrS in schizophrenia will be presented as an overview of general background information on BrS including its definition, and to summarize the existing evidence relating to BrS and schizophrenia. At the same time, our research question is broad enough to allow for expansive inclusion criteria for the search strategy. We aim to clarify important concepts in the field and explore relevant gaps in the literature – key indications for a scoping review [21].

This scoping review does not provide a critical appraisal of the literature, rather it provides a narrative summary of the identified information to aid in the exploring and understanding of different aspects of BrS in schizophrenia. In reporting the results in a narrative style, this study attempts to extrapolate and summarise data from a wide range of sources while providing evidenced-based guidance on the clinical management of patients with schizophrenia and the Brugada phenomenon.

2.1. Search strategy

We performed a systematic search of MEDLINE via PubMed, OVID, Web of Science, and Google Scholar with the terms: “schizophrenia and Brugada”, “schizophrenia and Brugada syndrome”, “schizophrenia and Brugada phenotype”, “antipsychotics and Brugada”, “psychotropics and Brugada”. The following words were also cross-referenced with the searches: “channelopathy”, “long QT”, “implantable cardioverter defibrillator”. Each search was performed with an unrestricted date range and unrestricted article type. The literature search covered all studies from inception up to July 2020. From this initial search we subsequently used lateral search strategies including scanning the reference lists of the retrieved articles and relevant review articles to identify relevant additional studies and searching websites known to be well established resources (brugadadrugs.org and brugadaphenocopy.com).

2.2. Inclusion criteria and data charting

Studies were included if they fulfilled the following criteria: presenting data on BrS and Brugada ECG patterns in schizophrenia regardless of study design; or described the epidemiology, clinical presentation, risk factors or management of BrS in schizophrenia. In terms of data charting, from our search this field of research is largely dependent on a small body of unsynthesized primary research articles, narrative reviews, and case reports. Three reviewers (AR, DVW, SA) screened all titles, abstracts and full texts independently and solved disagreements by consensus or consultation with a fourth reviewer (JL).

2.3. Search results

As shown in Fig. 1 the search produced 683 articles after removing duplicates and a final yield of 58 articles relevant to Brugada syndrome and the Brugada ECG pattern in schizophrenia were included. The included articles were categorised as follows: systematic reviews and meta-analyses (n = 11), task-force guidelines and consensus statements (n = 3), cohort studies (n = 13), case-control studies (n = 11), cross-sectional studies (n = 7), narrative reviews and editorials (n = 29), case reports (n = 21).

3. Epidemiology of Brugada syndrome in schizophrenia

To our knowledge, only one study has been conducted in multi-episode schizophrenia (86% (n = 236) treated with antipsychotic medication) to quantify the prevalence of the Brugada ECG pattern. This case control study found a prevalence of the Brugada ECG pattern of 11.6% (32/275) [12], significantly higher than in control groups and
strikingly higher than the published worldwide prevalence of 0.05% [22]. Only one patient had a true type 1 Brugada ECG pattern, but importantly, of the 23 patients with type 2 or 3 Brugada ECG pattern who consented to undergo ajmaline provocative testing, a further 10/23 developed the type 1 pattern. This supports the study findings that the prevalence of Brugada ECG pattern is a true finding, with type 2 and 3 Brugada ECG patterns being unexpectedly prevalent in people with schizophrenia.

A limitation of this study is that patients with normal baseline ECGs were not offered ajmaline testing, which means the true prevalence may be higher. Controls with Brugada ECG patterns were not offered ajmaline testing, although no type 1 Brugada ECG patterns were identified in the control group.

A case control study in recent onset schizophrenia estimated the odds ratio of having an ECG suspicious for Brugada ECG pattern to be 3.5 higher in those with schizophrenia (n = 23; mean age 22 years; 90% (n = 350) treated with antipsychotic medication) compared to healthy controls (n = 43; mean age 20 years) [13]. Of those with Brugada suspect patterns, 22 cases had ajmaline testing, with three displaying Brugada type 1 pattern, while eight controls were tested with one displaying Brugada type 1.

4. Brugada syndrome vs long QT syndrome

Both BrS and congenital long QT syndrome (LQTS) are ion channelopathies present in structurally normal hearts and can cause fatal ventricular arrhythmias, which can be precipitated by some psychotropic medications [23]. As congenital and acquired LQTS can induce similar ventricular arrhythmias as BrS in people with schizophrenia, it is important to distinguish the two. Table 1 details the major mutations causing both disorders. Fig. 2 shows a schematic comparison between BrS and LQTS.

The ECG patterns of LQTS and BrS are fundamentally different and reflect underlying electrophysiological dissimilarities. LQTS patterns include prolonged QT intervals and normal ST segments, whereas BrS presents with normal QT intervals and ST segment elevation [24]. Briefly, prolongation of action potentials in M-cells due to impaired INa and ICa is thought to cause QT prolongation and transmural dispersion of repolarization. These M-cells (mid-myocardial cells, also called “Moe” cells after their discoverer) have a longer action potential duration than epicardial and endocardial myocytes [24,25]. In BrS, there is also an increased transmural dispersion of repolarization, but it is due to impaired INa and ICa conduction in epicardial cells, not M-cells. It is interesting that both mechanisms can potentiate re-entrant polymorphic ventricular tachycardias, but via different mechanisms [24].

The most common, LQTS1 and LQTS2 are due to potassium channel mutations not implicated in BrS. It is important to note that the less common LQTS3 has Sodium Voltage-Gated Channel Alpha Subunit 5 (SCN5A) mutations.
5. Do Brugada syndrome and schizophrenia share common pathogenic elements?

As BrS is a channelopathy with multiple known genetic variants [27], it is possible that schizophrenia may share some pathogenic similarities. Nearly 300 mutations in SCN5A have been documented in BrS [28]. The voltage-gated sodium channel subunit encoded for by SCN5A is crucial for the fast depolarization of cardiomyocytes [29]. The BrS-1 SCN5A mutations differ from the LQTS SCN5A mutations; the exact mechanism of how the former relates to an elevated ST segment is not fully known [18,29].

Aberrant sodium conductivity has not figured as prominently as calcium dysregulation in schizophrenia. One large sequencing study discovered rare coding variants in multiple genes encoding for α-subunits of voltage-gated sodium channels in patients with schizophrenia [30]. However, among the ten known BrS mutations, the most common overlapping ones with schizophrenia are the calcium channel mutations, which have been reported in genome-wide association studies and meta-analyses alike [31–35].

Mutations in CACNA1C, which encodes the α-1C subunit of the L-type voltage-gated calcium channels have been heavily implicated in schizophrenia [34,36,37] and are present in 1–3% of BrS patients [27,34]. How this shared gene susceptibility manifests clinically is unknown at present. One important caveat to note when examining such genetic studies is that BrS patients are defined to have the SCN5A mutation as the quintessential inclusion criteria. This leaves comparative genomic studies between schizophrenia and BrP or the Brugada ECG pattern on its own simply lacking.

There is, however, evidence of decreased calcium channel conductivity in BrS, BrP, and the Brugada ECG pattern [18,38]. It is possible that the loss of the calcium channel current results in depleted intracellular calcium and loss of cardiomyocyte contractility. This may lead to a dilated right ventricular outflow tract (RVOT) and reduced ejection fraction, likely reflected in the different Brugada ECG types [18]. Furthermore, the loss of function SCN5A mutation impedes phase 0 entrance of sodium into cardiomyocytes (depolarization) and phase 2 efflux of sodium (plateau) – it is this gradient that allows calcium to
enter the cell via the sodium/calcium exchanger, but the lack of calcium influx would lead to weakened contractility [38].

Vitamin D deficiency, though not implicated in BrS to our knowledge, is prevalent in patients with schizophrenia [39–41] and may serve as an intermediary explanation for aberrant calcium channel conductivity. The expression of genes coding for L-type calcium channels (e.g. CACNA1C) are significantly linked to vitamin D concentrations [36,42]. Animal studies have demonstrated that vitamin D plays an integral role in modulating L-type calcium channels in the prefrontal cortex and hippocampus [36,42–44], two regions that have been strongly linked to cognitive impairment in patients with schizophrenia [45]. The direct relationship between vitamin D deficiency and BrS or Brugada ECG patterns is not yet substantiated, as the opposite may be true; both vitamin D toxicity from overdose [46] and over-expression of vitamin D binding protein [47] have been associated with Brugada ECG patterns.

It is unclear whether or not there is a subset of patients with schizophrenia who are genetically pre-disposed to BrS. Instead, a more common precipitant of the Brugada ECG patterns are psychotropic drug use.

6. Considerations for pharmacotherapy

It is well-documented that some antipsychotics may predispose to arrhythmias and SCD. Antipsychotic drug use has been associated with a 1.5-fold increase risk of ventricular arrhythmia and/or SCD in a nationwide cross-over study [48]. In terms of BrS specifically, a review by Sicouri and Antzelevitch [49] identified common psychotropics that may induce Brugada type 1 ECG patterns.

Elaborating on this, Postema and colleagues [50] compiled a comprehensive list of drugs stratified by likelihood of Brugada ECG pattern induction or unmasking displayed in a user-friendly website brugadadrugs.org. This is a significant step in the accessibility and centralization of information in an effort to help psychiatrists, cardiologists, and primary care physicians manage emerging Brugada ECG patterns. Amitriptyline, clomipramine, desipramine, lithium, loxapine, nortriptyline, oxcarbazepine and trifluoperazine have all been placed on the “Drugs to be Avoided – Strong Recommendation” list, while thioridazine, fluoxetine, paroxetine, lamotrigine, and carbamazepine are among those on the “Drugs to be Avoided – Weak Recommendation” list. See Table 2 for a list of psychotropics.

Table 2
Brugada ECG inducing psychotropic drugs to avoid and use with caution in patients with schizophrenia. See brugadadrugs.org for a full list of other drugs classes.

| Antidepressants | Avoid – strong recommendation | Avoid – weak recommendation |
|-----------------|-------------------------------|-----------------------------|
| SSRIs           | Paroxetine                    | Fluoxetine                  |
|                 |                               | Fluvoxamine                 |
| SNRIs           | Amitriptyline                 | Imipramine                  |
| TCAs            | Clomipramine                  | Desipramine                 |
|                 | Desipramine                   | Nortriptyline               |
|                 |                               | Maprotiline                 |
| NDRIs           |                               | Bupropion                   |
| Antipsychotics  |                               |                             |
| First generation| Thioridazine                  | Perphenazine                |
|                 | Trifluoperazine                | Clozapine                   |
|                 |                               | Cyamemazine                 |
|                 |                               | Thioridazine                |
| Second generation|                               | Lamotrigine                 |
| Mood stabilizers| Lithium                       | Carbamazepine               |

Tricyclic antidepressants (TCAs), like imipramine, and selective serotonin reuptake inhibitors (SSRIs), like fluoxetine, impair cardiac conduction by blocking INa, ICa, and IK currents [23]. While IK inhibition has been linked to LQTS, as described earlier, exacerbated with antipsychotic use, INa and ICa inhibition has been linked to BrS. Fluoxetine binds to the same voltage-gated sodium channel site as Class IA anti-arrhythmics [51]. Class 1A anti-arrhythmics such as procainamide augment ST segment elevation via IK blockade, thereby decreasing action potential duration in the epicardium [26]. Several case studies have demonstrated Brugada ECG patterns from TCA overdose as well [52–54]. TCA administration at therapeutic doses can also induce Brugada pattern ST segment elevation and mimic Class 1A anti-arrhythmic effects [55]. Case studies have revealed lithium can elicit Brugada ECG patterns [56–59], possibly due to IK inhibition as well [56].

The phenothiazine sub-class of typical antipsychotics exert similar proarrhythmic affects as quinidine [60]. These include trifluoperazine, thioridazine [61], and perphenazine – all of which are listed as drugs to be used with caution due to BrS unmasking potential. A similar mechanism of IK inhibition can result in an abbreviated action potential duration and may manifest as the Brugada pattern ST segment elevation [60]. The predominant proarrhythmic effect of typical and atypical antipsychotics, however, seems to arise from IK blockade mediated QT prolongation [23]. To our knowledge, atypical antipsychotics have not been definitively shown to unmask BrS. Two exceptions, though more substantiating data is needed, may be clozapine and risperidone. Neither are listed in the brugadadrugs.org registry, which contains a collection of case reports on psychotropic precipitants of Brugada ECG patterns. A case report by Sawyer and colleagues [62] identified Brugada ECG patterns in a patient shortly after clozapine initiation, with the effect disappearing after cessation of the drug. Chong and Everheim [63] describe the case of a 49-year-old with schizophrenia showing clozapine-induced Brugada ECG patterns. Ukaigwe and colleagues [64] also document a 49-year-old who developed the Brugada type 1 ECG pattern after initiation of clozapine, which resolved within 24 h after discontinuation. Finally, Laboudi and colleagues [65] report risperidone (4 mg/d) induced a Brugada type 1 ECG pattern in a 25-year-old with schizophrenia, with no cardiac history or familial history of sudden cardiac death. Discontinuation of risperidone resolved the abnormal ECG [65].

Two uncertainties arise from these case reports. First, it remains questionable whether second-generation antipsychotics induce a Brugada ECG pattern or unmask the BrS itself. Second, the mechanism by which clozapine and risperidone may cause such an effect is unknown. There is evidence that clozapine inhibits T-type calcium channels in human kidney cells [66] and inhibits serotonin-induced calcium conductivity but increases overall intracellular calcium concentrations in rat glioma cells [67]. This calcium channel modulation may play a role in unmasking the Brugada ECG pattern, but this remains speculation.

7. Management of patients with schizophrenia and Brugada syndrome

7.1. Asymptomatic Brugada syndrome

As many as 67% of patients with BrS are asymptomatic [16]. These patients typically present with the Brugada ECG pattern with few if any clinical features. Currently this cohort of patients is not recommended to receive an implantable cardioverter defibrillator (ICD). While their risk of arrhythmic incident is not negligible [68], it is important to carry out risk stratification to determine if the potential benefits of an ICD implantation outweigh the significant comorbidities and long-term effects of the device. Typically, patients diagnosed with BrS are quite young and the long-term risk of device-related complications is significant [69]. No randomized trials have been conducted as of yet.
comparing asymptomatic patients receiving no treatment to those receiving pharmacological treatment or ICD implantation. Risk stratification can be quite complicated in asymptomatic BrS due to lack of consensus. However, spontaneous type 1 ECG patterns, inducible ventricular arrhythmias and sinus node dysfunction are associated with an increased risk of incidents [70–72]. Patients showing these risk factors may benefit from ICD implantation [16].

7.2. Symptomatic

7.2.1. Pyrexia

Fever can unmask a Brugada ECG pattern in genetically susceptible patient populations [73] which may normalise upon resolution of the fever with antipyretics [74]. Fever-induced BrS may become increasingly relevant in the COVID-19 pandemic, as SARS-CoV2 has been reported to unmask the Brugada ECG pattern [75,76]. This may suggest that psychiatric patients are at a particular risk should they be infected with SARS-CoV2 due to the increased prevalence of BrS and the Brugada ECG pattern in patients with schizophrenia.

7.2.2. Drug-induced

Any person diagnosed with BrS should be advised on the avoidance of the following psychotropics: amitriptyline, clomipramine, desipramine, lithium, loxapine, nortriptyline, oxcarbazepine, trifluoperazine and others (See Table 2). Psychiatric patients who present with concerning cardiac symptoms of arrhythmias, such as syncope, may warrant BrS to be considered as a potential underlying cause and may require input from a cardiologist [77]. Psychotropic dose adjustments, switching drug classes, avoiding high dose antipsychotic use and polypharmacy, as well as minimising other risk factors such as drug to drug interactions [78], electrolyte abnormalities (e.g. hypokalemia) [79] and avoiding cocaine use, all mitigate the risk of SCD.

8. Treatment options

The ICD remains first line treatment for BrS [80]. The use of ICDs has led to reduced mortality rates in symptomatic patients with BrS. In asymptomatic patients, however, the benefit of an ICD is outweighed by the associated long-term risks including multiple procedures and inappropriate shocks [81]. Patients who show spontaneous type 1 ECG patterns as well as two other accepted risk factors, such as syncope or familial SCD should be immediately considered for an ICD [82]. VF inducible through electrophysiological tests is another indication, although controversial [83]. While ICD implantation is the first line treatment of BrS, it is unfortunately not always suitable or indeed available for certain patients [84]. The age of the patient must be considered when deciding on ICD implantation. As the BrS pattern is typically identified in early life, ICD-users are faced with several decades of potential complications [85]. Moreover, ICDs do not prevent the recurrence of VF or VTs but instead deliver shocks in response to the ventricular arrhythmias to prevent SCD.

Some BrS patients that fall into the high-risk category, experience frequent episodes of VF leading to the electrical storm phenomenon [86] requiring multiple ICD discharges. In such patients, radiofrequency catheter ablation can reduce the chances of further VF from occurring via removal of arrhythmia causing complexes [87]. Through mapping of abnormal epicardial areas, in particular the right ventricular outflow tract [88], aided by amjaline administration [89], ablation can decrease the recurrence of ventricular arrhythmias. To our knowledge, quinidine is the only pharmaceutical medication that has been proven successful in reducing the chances of malignant arrhythmia and electrical storm in BrS patients [90,91]. Quinidine has potential as a safe alternative to ICD implantation in those not deemed as suitable for implantation [92] or as an adjuvant therapy for patients that have already received an ICD [91,93].

Brojmohun and colleagues have developed an algorithm for psychiatrists managing patients with ICDs [94]. First, an evaluation of baseline risk factors including electrolyte imbalances and a medication review of pro-arrhythmic psychotropics and medications associated with BrS must be conducted. Second, a baseline ECG, manual measurements of QTc intervals, and dose optimization of psychotropics should be completed. As BrS most often presents with ST segment elevation, we recommend checking for this ECG abnormality. Telemetry monitoring and repeat ECGs post-psychotropic initiation and titration should also be considered. A careful risk and benefit analysis is required for the continued use of a pro-arrhythmic psychotropic medication and the increased risk of an ICD discharging.

Finally, it is important to consider the psychological implications of ICDs may have for people with schizophrenia. Post-implantation depression and anxiety can be exacerbated by lack of social support and incomplete patient understanding of how their ICDs are calibrated [95,96]. Shock expectancy, shock unexpectancy, and fear of inappropriate shocks are just a few of the anxiety provoking issues affecting ICD patients [95,97]. One study of ICDs in BrS patients found that ICDs are associated with significant negative impacts on social and professional life [98]. While not studied in patients with schizophrenia, it stands to reason that the risk may be magnified in those with pre-existing functional impairments. Devising novel ways to address these issues will be crucial, as ICDs remain the only effective long-term therapy for recurrent malignant arrhythmias. These may include integrated approaches to care, with collaboration between cardiology and psychiatry to provide a careful risk and benefits assessment for the treatment intervention. Collaborative approaches to patient education regarding ICDs, and the provision of additional multidisciplinary support from allied health professionals may all contribute to facilitating the successful implementation of an ICD and reduce the psychological impact. ICDs also require regular checks and cardiac medications to reduce the number of inappropriate shocks, making compliance another potential issue [99].

9. Limitations

In this scoping review we sought to clarify key concepts and ambiguous terminology and analyze specific knowledge gaps that may provide translatable clinical insights. Several limitations of this study exist. First, there is limited data on BrS and the Brugada ECG pattern in schizophrenia. There were no controlled studies available and there is a need for caution in interpreting data relating to case reports and case series. Case reports and theoretical conclusions from narrative reviews alone cannot provide an accurate or quantitative measure of the risk for complications or death associated with BrS and Brugada ECG patterns in schizophrenia. A publication bias in favor of cases in which discontinuation of antipsychotics was associated with a resolution of the Brugada ECG pattern is possible. Furthermore, unreported deaths due to unmasked Brugada ECG patterns by antipsychotic therapy should be considered.

A consequence of the emphasis on case reports presents imperfections in the risk-stratification of different psychotropics that may not provide findings generalizable to standard psychotropic prescribing and use. The list of drugs in the Avoid – Strong Recommendation and Avoid – Weak Recommendation are largely based on such case reports. However, with new repositories such as brugadadrugs.org, the hope is that increased awareness and reporting of BrS and Brugada ECG pattern cases in schizophrenia will ensure a wider data pool from which clinical recommendations can be made. Despite this, we have provided a comprehensive review of the definition and diagnosis, epidemiology, risk factors for and management of BrS in schizophrenia. There remains a clear need for further research to provide data on epidemiology, pathophysiology and treatment of BrS and the Brugada ECG pattern in schizophrenia.
10. Conclusions

10.1. Key points in pathophysiology

BrS and BrP are under-recognized cardiac disorders in patients with schizophrenia. Ion channel abnormalities in BrS, especially sodium and calcium conductivity, can significantly pre-dispose to malignant arrhythmias. The unmasking of Brugada ECG patterns by commonly prescribed psychotropics that modulate sodium and calcium potentiation may also lead to SCD independent of prolonged QT. While psychiatrists may be more familiar with LQTS, it is important to recognize BrS and BrP as additional SCD risk factors that can lead to the same outcome via different mechanisms.

10.2. Key points in management

People with schizophrenia may benefit from ECG screening for the Brugada ECG pattern and those diagnosed with definite or potential BrS require cardiology input to provide expert guidance on treatment.

- Close collaboration with cardiology
- Baseline psychotropic medication review and dose optimization
- Baseline and serial ECGs following titration of psychotropics
- Manual measurement of QTc
- Monitoring for ST segment elevations

Interventions should be personalized to each patient in consideration of comorbidities and current medication regimens. ICDs are the only recommended treatment for those at risk of fatal arrhythmia from BrS. Meaningful interventions to reduce risk factors for BrS and SCD require early implementation. This will involve removing system barriers to adequate and timely medical care, and fostering collaborative approaches between primary care, psychiatry and cardiology. People with BrS should be advised to avoid proarrhythmic medications, and not to use medications on the “Avoid – Strong Recommendation” and “Avoid – Weak Recommendation” lists.

The prevalence and long-term prognosis of individuals with the Brugada ECG pattern in schizophrenia is unknown, and the clinical course and prognosis of BrS and those with Brugada ECG patterns in this population remains unclear. Large scale prospective studies are required to establish the prevalence of and clinical course for BrS and Brugada ECG patterns in schizophrenia.

Author contributions

JL and AR first conceptualized the idea for the review. AR, DVW, SA, and JL created an outline for which the methodology was based. AR, DVW, SA, and JL devised the search strategy used to curate relevant literature for the review. AR, DVW, SA, and JL wrote the initial draft, which went through numerous iterations and rounds of editing by FG and NG. All authors reviewed and edited the final version of the draft.

Disclosures

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References

[1] Correll CU, Solmi M, Veronese N, Bortolato B, Rossan S, Santonastaso P, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 115,383,368 controls. World Psychiatry 2017;16:163–80. https://doi.org/10.1002/wps.20420.
[2] Walker ER, McGee RE, Druss BG. Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. JAMA Psychiatry 2015;72:334–41. https://doi.org/10.1001/jamapsychiatry.2014.2562.
[3] Westman J, Eriksson SV, Gissler M, Hallgren J, Prieto ML, Boho VW, et al. Increased cardiovascular mortality in people with schizophrenia: a 24-year national register study. Epidemiol Psychiatr Sci 2018;27:519–27. https://doi.org/10.1017/9.
Sonoda K, Watanabe H, Hisamatsu T, Ashihara T, Ohno S, Hayashi H, et al. High Kapplinger JD, Tester DJ, Alders M, Benito B, Berthet M, Brugada J, et al. An in- Wilde AAM, Amin AS. Clinical spectrum of SCN5A mutations: long QT syndrome, Moskvina V, Craddock N, Holmans P, Nikolov I, Pahwa JS, Green E, et al. Gene- and cardiac syndrome, and cardiomyopathy. JACC Clin Electrophysiol 2018;4:569-79. Gooch H, Cui X, Anggono V, Trzaskowski M, Tan MC, Eyles DW, et al. 1,25-

Brewer LD, Thibault V, Chen K-C, Langub MC, Landfield PW, Porter NM. Vitamin D and implicates voltage-gated sodium channels in schizophrenia pathogenesis. Biol Brewer MAR, O’Donovan MC, Meng YA, Jones IR, Ruderfer DM, Jones L, et al. Risk alleles for schizophrenia and bipolar disorder and for overlap in genetic risk. Mol Psychiatry. 2011;24:78–85. https://doi.org/10.1038/mp.2009.148.

Ferreira MAR, O’Donovan MC, Meng YA, Jones IR, Ruderfer DM, Jones L, et al. Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. Nat Genet 2008;40:1056–8. https://doi.org/10.1038/ng.209.

Neygaard M, Demontis D, Foldager L, Hedemand A, Flint TJ, Sørensen KM, et al. CACNA1C (rs1006737) is associated with schizophrenia. Mol Psychiatry 2009;14:252–60. https://doi.org/10.1038/mp.2008.133.

Adler A, Topaz G, Heller K, Zeltser D, Ohayon T, Rozovski U, et al. Fever-induced CACNA1C (rs1006737) is associated with schizophrenia. Mol Psychiatry 2009;14:252–60. https://doi.org/10.1038/mp.2008.133.

Moskvina V, Craddock N, Holmans P, Nikolov I, Pahwa JS, Green E, et al. Gene-

Gooch H, Cui X, Anggono V, Trzaskowski M, Tan MC, Eyles DW, et al. 1,25-

Brewer LD, Thibault V, Chen K-C, Langub MC, Landfield PW, Porter NM. Vitamin D and implicates voltage-gated sodium channels in schizophrenia pathogenesis. Biol Psychiatry 2019;85:554–61. https://doi.org/10.1016/j.biopsycho.2018.08.022.

Dedic N, Pöhlmann ML, Richter JS, Mehta D, Czamara D, Metzger MW, et al. Cross-
disorder risk gene CACNA1C differentially modulates susceptibility to psychiatric disorders during development and adulthood. Mol Psychiatry 2018;23:533–43. https://doi.org/10.1038/mp.2017.133.

Jiang H, Qiao F, Li Z, Zhang Y, Cheng Y, Xu X, et al. Evaluating the association between CACNA1C rs1006737 and schizophrenia risk: a meta-analysis. Asia Pac Psychiatry 2015;7:260–7. https://doi.org/10.1111/appy.12171.

Bipat S, Dubilane Gobert M, Camerini K, Morin M, Alkert S, et al. Genome-
wide association identifies 13 new risk loci for schizophrenia. Nat Genet 2013;45(10):1150–9. https://doi.org/10.1038/ng.2742.

Zhu D, Yin J, Liang C, Luo X, Li D, Dai Z, et al. CACNA1C (rs1006737) may be a susceptibility gene for schizophrenia: an updated meta-analysis. Brain Behav 2019;9. https://doi.org/10.1002/brb3.1292.

Hertzberg L, Katz S, Roussos P, Haroutunian V, Duman E. Integration of gene expression and GWAS supports involvement of calcium signaling in schizophrenia. Schizophr Res 2015;164:92–9. https://doi.org/10.1016/j.schres.2014.11.014.

Ferreira MAR, O’Donovan MC, Meng YA, Jones IR, Ruderfer DM, Jones L, et al. Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. Nat Genet 2008;40:1056–8. https://doi.org/10.1038/ng.209.

Neygaard M, Demontis D, Foldager L, Hedemand A, Flint TJ, Sørensen KM, et al. CACNA1C (rs1006737) is associated with schizophrenia. Mol Psychiatry 2010;15:119–21. https://doi.org/10.1038/mp.2009.69.

Monasky MM, Pappone C, Piccillo M, Girolidi A, Micaglio E, Anastasia L. Calcium in Brugada syndrome: questions for future research. Front Physiol 2018;9. https://doi.org/10.3389/fphys.2018.01088.

Adamson J, Lally J, Gaughran F, Krivoi A, Allen L, Stubbs B. Correlates of vitamin D in psychotic disorders: a comprehensive systematic review. Psychiatry Res 2017;249:78–85. https://doi.org/10.1016/j.psychres.2016.12.052.

Lally J, Gardiner-Sood M, Lybeek C, Stubbs B, Greenwood K, et al. Clinical correlates of vitamin D deficiency in established psychosis. BMC Psychiatry 2016;16:76. https://doi.org/10.1186/s12888-016-0780-2.

Dong Y, Kikuya T, Ogasawara H, Iwasa M, Sugiyama S, et al. Risk of sudden death in patients with Brugada syndrome on implantable cardioverter-defibrillator therapy: a 20-year follow-up study. Europace 2013;15:1741–7. https://doi.org/10.1093/europace/eut243.

Dong Y, Kikuya T, Ogasawara H, Iwasa M, Sugiyama S, et al. Risk of sudden death in patients with Brugada syndrome on implantable cardioverter-defibrillator therapy: a 20-year follow-up study. Europace 2013;15:1741–7. https://doi.org/10.1093/europace/eut243.

Dong Y, Kikuya T, Ogasawara H, Iwasa M, Sugiyama S, et al. Risk of sudden death in patients with Brugada syndrome on implantable cardioverter-defibrillator therapy: a 20-year follow-up study. Europace 2013;15:1741–7. https://doi.org/10.1093/europace/eut243.

Dong Y, Kikuya T, Ogasawara H, Iwasa M, Sugiyama S, et al. Risk of sudden death in patients with Brugada syndrome on implantable cardioverter-defibrillator therapy: a 20-year follow-up study. Europace 2013;15:1741–7. https://doi.org/10.1093/europace/eut243.
syndrome. Case Rep Psychiatry 2014;2014:1–4. https://doi.org/10.1155/2014/478397.

[78] Strain JJ, Kairim A, Caliendo G, Alexis JD, Lowe 3rd RS, Fuster V. Cardiac drugpsychotropic drug update. Gen Hosp Psychiatry 2002;24:283–9. https://doi.org/10.1016/s0163-8343(02)00184-6.

[79] Lam MH, Chau SW, Wing Y. High prevalence of hypokalemia in acute psychiatric inpatients. Gen Hosp Psychiatry 2009;31:262–5. https://doi.org/10.1016/j.genhosppsych.2009.02.007.

[80] Dereci A, Yap SC, Schinkel AFL. Meta-analysis of clinical outcome after implantable cardioverter-defibrillator implantation in patients with Brugada syndrome. JACC Clin Electrophysiol 2019;5:141–8. https://doi.org/10.1016/j.jacep.2018.09.005.

[81] Kaeppler M, Kapoor R, Oujiri J. Brugada syndrome in a young patient: to recommend an ICD or not to recommend an ICD? J Am Coll Cardiol 2019;73:2332. https://doi.org/10.1016/j.jacc.2019.07.022.

[82] Pellegrino PL, Di Biase M, Brunetti ND. Quinidine for the management of electrical storm in an old patient with Brugada syndrome and syncope. Acta Cardiol 2013;68:201–3. https://doi.org/10.1080/03634425.2013.768747.