Background: Juvenile myoclonic epilepsy (JME) is referred to as one of the most common epileptic syndromes. Several anti-epilepsy drugs (AEDs) have been developed and remain part of clinical intervention with varying safety and efficacy profiles. Comprehensive synthesis of the scientific evidence examining the safety and efficacy of clonazepam toward the treatment of JME was carried out in the study. Methods: A detailed scientific literature search was made utilizing the most relevant scientific studies published to date on the intervention of clonazepam in the management of JME. In this study, a detailed search was made in multiple databases, including PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and Scielo databases. Confidence intervals among the studies and continuous measures, proportion, and risk factor analysis were determined using the MedCalC tool (Version 20.110) as per PRISMA guidelines. Results: A total of 6 studies out of 70 were found eligible for meta-analysis, where 186 JME patients were subjected to clonazepam intervention with controls. Clonazepam was reported effective in comparative analysis among six studies where \( P < 0.001 \). The result also shows a higher prevalence of JME in the female population compared to males (male versus female; 86/110). Efficacy and safety of clonazepam were reported significant as well. Conclusion: Clonazepam is effective AEDs for the management of JME. However, more clinical evidence requires for statistical validation of clinical efficacy. Keywords: Anti-epilepsy drugs, confidence interval, juvenile myoclonic epilepsy (JME), meta-analysis, odd ratio

Department of Pharmacy Practice, College of Pharmacy, Shaqra University, Al-Dawadmi, Saudi Arabia

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INTRODUCTION

Juvenile myoclonus epilepsy (JME) is defined as an idiopathic epileptic syndrome. The etiology of JME remains unknown and sometimes determined via genetic analysis.[1] JME is a generalized epileptic syndrome with significantly higher prevalence in the epileptic subjects, that is, 5–11% and between 0.5 and 1.0% out of 1000 in a given population.[2] As per the International League against Epilepsy (ILAE), JME is the most common epileptic syndrome not only in epileptic subjects but also in the general population. The prevalence of JME is considerably higher in female over male epileptic subjects in a given population.[3] The precise cause and age of JME onset are not clear, but increasing research evidence suggests an adolescent age where syndrome symptoms are reported the first time.

The clinical diagnosis of JME varies among physicians; however, a standard approach to diagnosis depends on early-morning myoclonic seizures (MC).[4] The MC may be alone and or in combination with other types of seizures, including generalized tonic-clonic seizures and less frequent absences. Clinically diagnosed JME patients also demonstrate interictal generalized spike-wave discharges (SWDs) and normal background activity.[5] Electro-encephalography (EEG) remains an important and robust tool to diagnose the state of JME in epileptic subjects and also in the normal population.[6]

Address for correspondence: Dr. Faisal Al-Otaibi, Department of Pharmacy Practice, College of Pharmacy, Shaqra University, Al-Dawadmi, P. O. BOX 33, Saudi Arabia, E-mail: f.alotaibi@hotmail.com

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As mentioned above, the precise cause of JME remains unknown; however, recent findings have demonstrated that genetics may play a vital role in the onset and progression of the syndrome.⁷ Recent studies have demonstrated that several causative/susceptibility genes are associated with early onset and progression of JME. The genes linked with JME such as CACNB4 (calcium channel, voltage-dependent, beta 4 subunit), CASR (calcium-sensing receptor), GABRA1 (gamma-aminobutyric acid A receptor, alpha 1), GABRD (gamma-aminobutyric acid A receptor, delta), and EFHC1 (EF-hand domain (C-terminal) containing 1) were studied recently and reported a close association because of abnormal expression levels.⁸⁻¹⁰ Santos et al., 2017¹¹ demonstrated a non-mandolin approach to establish a link between listed genes and JME. The study has also shown that genetic polymorphisms such as rs2029461 SNP in GRM4, rs3743123 in CX36, and rs3918149 in BRD2 serve as a critical factor here. However, such studies are limited, and hence, these studies may not be significant to conclude a scientific argument. The anti-epileptic drug (AED) intervention offers the most effective and robust treatment for epilepsy and JME. As a broad-spectrum anti-epilepsy drug, valproic acid has been used extensively in the past for the management of epileptic syndromes, including JME.¹² Valproic acid is also associated with teratogenic potential, and hence, clinical use of the drug is restricted during pregnancy.

Several other anti-epileptic drugs were developed and used in the management of epileptic syndromes, such as levetiracetam, lamotrigine, topiramate, and zonisamide.¹³ The clinical use of the anti-epilepsy drug also depends on types of epileptic syndrome and severity as well. For example, lamotrigine remains a potential anti-epilepsy drug for JME; however, it causes worsening in myoclonic seizures.¹⁴ The use of ethosuximide is more specific in the case of absence seizures. Several other anti-epileptic drugs such as carbamazepine, oxcarbazepine, and phenytoin remain in clinical use but are associated with severe complications such as exacerbating myoclonic and absence seizures contraindicated.¹⁵ Clonazepam (benzodiazepine) is an effective AED and enhances the neuro-inhibitory activity of GABA. Clonazepam use is specific and reported effective in controlling myoclonic jerks. However, the clinical uses of clonazepam do not respond against generalized tonic-clonic seizures (GTCSs).¹⁶ Several studies have demonstrated that the clinical uses of clonazepam in the management of JME are effective with variations in the safety profile.⁹ The studies have also shown a varying effect of clonazepam in studied populations across the globe. Hence, the current study aimed to analyze the safety and efficacy of the existing clinical interventions that used clonazepam for JME management.

**Materials and Methods**

**Search strategy and study selection**

The present study aimed to carry out a meta-analysis as per PRISMA statement/guidelines. To achieve aimed objectives, database search was made for the literature including clinical studies till September 2021. In this study, various databases, including PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and Scielo databases, were investigated and explored. A detailed examination was performed for the most relevant scientific outcome studies, with clonazepam in the management of JME. Multiple databases and resources were accessed to examine pertinent studies, mainly randomized clinical trials (RCTs), meta-analyses, and expert opinion. Furthermore, several specific searches in various databases were made for a close association between clonazepam and the treatment of juvenile myoclonic epilepsy in context with safety and efficacy, emphasizing our particular aim and objectives. Studies associated with RCTs and meta-analysis were incorporated. Different search keywords were used in accessing key clinical studies. In the search, multiple keywords were used, including “clonazepam and juvenile myoclonic epilepsy,” “juvenile myoclonic epilepsy and therapies,” “clonazepam and uses,” “interventions of clonazepam,” “juvenile myoclonic epilepsy management,” “safety of clonazepam,” and “efficacy of clonazepam.” The search using individual and combination keywords was performed in various databases. For the most relevant studies, a combination of keywords was used in the literature search from different databases. Furthermore, search keywords, including RCTs, meta-analysis, and clinical findings, were used for study design, protocol, and participants. Pre-defined inclusion and exclusion criteria were applied for screening of most relevant studies for meta-analysis.

**Inclusion/exclusion criteria**

Table 1 summarizes inclusion and exclusion criteria used for the screening of the literature. The present study primarily considered RCTs explicitly in the synthesis of the hypothesis for the involvement of clonazepam in the management of JME. Most relevant studies screened for meta-analysis based on inclusion and exclusion criteria considered for the analysis and synthesis of theories from English languages only. Furthermore, studies not defined completely and such studies poorly defined and/or such studies with abstract only were not included for meta-analysis. Here, in the present...
study, the eligible studies were also subjected to publication bias analysis. Publication biasness was also considered while applying inclusion and exclusion criteria. Using Egger’s test, biasness in publication was evaluated, where the citation of publication results in the likelihood of being included in the meta-analysis.

Data extraction and bias assessment
Bias assessment was performed as per the PRISMA statement, and data from the most eligible studies were retrieved. Data comprised the study population, the prevalence of JME in males and females, intervention (dose of clonazepam, route of intervention), and control (other AEDs or placebo). The safety and efficacy data are based on the absence of symptoms after intervention and the follow-up period in each study.

Meta-analysis
The retrieved scientific information was used to analyze and interpret the safety and efficacy of clonazepam therapeutic and efficacy profiles in the management of JME. MedCalC tool Version 20.110 (https://www.medcalc.org/) was used for meta-analysis using studies screened based on inclusion and exclusion criteria. In the present study, three different parameters were used for the meta-analysis, including continuous measures, proportion, and risk factor analysis. In the meta-analysis, three different variables (clonazepam alone and combined with other AEDs or placebo) were considered for studies published until September 2021. Analysis was carried out for significance level using continuous measure, proportion, and risk analysis. Here, the 95% confidence interval (CI) and standard error (SE) were determined using studies, qualified based on inclusion and exclusion criteria. The analysis was made to establish effectiveness with pharmacokinetic (ADME properties) and pharmacokinetic properties (therapeutic and toxic effects). To synthesize a valid scientific argument, the study precisely focuses on RCT studies carried out recently. The inclusion and exclusion criteria were considered during the analysis as well. The results were interpreted under PRISMA guidelines. Additionally, the study also emphasizes limitations during the retrieval of scientific information and its impact on our study.

RESULTS
Here, 70 original studies were collected from various databases, including PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and Scielo. Among these, 64 original studies from different databases and six from other resources were included for the screening process. A total of 34 were excluded from the screened record as not found relevant to aimed objectives. Furthermore, three more studies were excluded as reported duplicates from the pool. Subsequently, 27 more studies were excluded, which do not abide by eligibility criteria and publication bias analysis. The inclusion and exclusion criteria were applied, and six most eligible articles were found. The selection of studies is based on the intervention of clonazepam in clinically diagnosed JME patients. Meta-analysis was performed based on the six most eligible studies. A detailed search strategy and study selection are shown in Figure 1 as per the PRISMA statement. Tables 1 and 2 provide clinical data from the most relevant studies. Here, in Table 1, all six eligible studies have shown a higher prevalence of JME in the female population compared to males. Furthermore, Table 2 demonstrates the safety and efficacy profile of clonazepam, and data were retrieved and interpreted considering controlling myoclonic jerks.

Here, efficacy was determined via the lack of re-occurrence of myoclonic seizures in JME subjects. As a result, as shown in Figure 2, the odds ratios demonstrate a total random effect between 3 and 60 but a relative risk between 1 and 10. Furthermore, the risk difference was calculated with a random effect lies between 0.2 and 0.7. Previous studies have also

### Table 1: Criteria followed in the present study

| Criteria                  | Characteristics                                                                 |
|---------------------------|----------------------------------------------------------------------------------|
| Inclusion Criteria        |                                                                                |
| Outline                   | RCTs                                                                            |
|                           | Studies that provide interventional details of clonazepam in the management of JME. |
| Patients                  | JME undergone for clonazepam intervention.                                      |
| Intervention              | Clonazepam and placebo or other AEDs                                            |
| Language                  | English                                                                         |
| Exclusion Criteria        | Poorly explained and/or incomprehensible methodology                            |
| Publication Method        | Abstract only                                                                   |

### Table 2: Summary of eligible studies based on inclusion and exclusion criteria. Study population and study set-up including intervention dose with control and other AEDs

| Study                   | Study Population | Male/ female | Control | Clonazepam dose |
|-------------------------|------------------|--------------|---------|-----------------|
| Rafiei, 2009            | 15               | 6/9          | 16 valproate  | 1.0-4.0 mg      |
| Panayiotopoulos et al., 1994 | 66             | 33/33     | 66 Placebo | 1.0-4.0 mg      |
| Machado et al., 2013    | 38               | 14/24       | 17 Placebo | 1.1 mg          |
| Prasad et al., 2003     | 35               | 16/19       | 35 Placebo | 1.0-4.0 mg      |
| Dreifuss et al., 1975   | 10               | --          | 10 Placebo | 0.028 to 0.111 mg |
| Fazio et al., 1975      | 32               | 17/25       | 25 Placebo | 0.1-0.5 mg      |
shown a high re-occurrence rate of myoclonic jerks in the control group (without clonazepam intervention). However, generalized seizures remain a major limitation for clonazepam universally reported in all six studies. The data shown in Table 3 demonstrate varying CI values and weight % among the six eligible studies used for meta-analysis. The present meta-analysis provides a scientific basis for the effectiveness of clonazepam as an AED as the P value remains significant (p < 0.001) [Supplementary Table 1]. A similar pattern was reported during relative risk and risk difference analysis. Hence, clonazepam is effective in controlling myoclonic jerks and JME but non-effective in controlling generalized seizures. The test for heterogeneity (inconsistency I^2) and the significance level reported 73.19% and \( P = 0.0022 \) in odds ratio analysis. Publication bias was also performed via Eggers test and Begg test for Kendall Tau analysis. An intercept of -1.7214 with 95% CI was reported in publication bias analysis -17.0842-13.64 with a significance level of \( P = 0.7713 \) [Supplementary Table 2]. The significance level was much higher for the Begg test, with \( P = 0.3476 \) and a Kendall tau of -0.333 [Supplementary Table 3].

**Discussion**

JME is a common idiopathic epileptic syndrome with high prevalence, that is, 5–15% among epileptic subjects and 0.5–1.0% in the general population. A series of AEDs have been developed and being used for the management of JME. It has been reported that AEDs remain associated with several complications, including teratogenic effects. Clonazepam is a chlorinated derivative of nitrazepam, a crucial AED for the management of JME. The drug is well absorbed with the large volume of distribution. Like other benzodiazepines,

| Study             | Study Population | Control  | Clonazepam | Safety and efficacy |
|-------------------|------------------|----------|------------|---------------------|
| Rafiei, 2009      | 15               | 16 valproate | 1.0-4.0 mg | 90%                 |
| Panayiotopoulos et al., 1994 | 66               | 66 Placebo | 1.0-4.0 mg | 72%                 |
| Machado et al., 2013 | 38               | 17 Placebo | 1.1 mg | 80%                 |
| Prasad et al., 2003 | 35               | 35 Placebo | 1.0-4.0 mg | 90%                 |
| Dreifuss et al., 1975 | 10               | 10 Placebo | 0.028 to 0.111 mg | 85% |
| Fazio et al., 1975  | 32               | 25 Placebo | 0.1-0.5 mg | 68%                 |

Figure 1: PRISMA flow diagram demonstrating the search strategy and study selection (http://prisma-statement.org/)

Table 3: Summary of the safety and efficacy profile of clonazepam among various studies based on frequency and severity of seizures
Clonazepam had a slower elimination rate (both hepatic and renal) and controlled mood disorders during epileptic seizures \cite{18-21}. Benzodiazepine as an anti-convulsant offers a wide range of applications, including management of various types of epilepsy, including JME. Additionally, clonazepam plus valproate sodium significantly improved median scores for myoclonus, general performance, and locomotor ability compared to baseline values \cite{22,23}. Clonazepam is one of the most effective AEDs precisely for JME management but is also associated with complications. Rafiei, 2009 had shown the superiority of clonazepam over valproic acid \cite{17,24}. The efficacy was reported to be 96\%, where clonazepam was reported effective in controlling myoclonic jerks. However, clonazepam does not provide any significant benefits in controlling generalized seizures. Compared to the control group (treated with valproic acid), a high re-occurrence rate among the group was reported (87.5\%). Earlier, Panayiotopoulos, 1994 demonstrated similar findings in a 5-year prospective study. The result shown in the study demonstrated that more than 70\% of JME patients did not show any re-occurrence (myoclonic jerks) under the intervention of clonazepam \cite{2,18}. The study also showed steady-state generalized seizures in the intervention group despite treatment with clonazepam. The study also demonstrates that female epileptic subjects diagnosed a higher percentage compared to males for JME. Other four studies included in meta-analysis studies also...

Figure 2: (a) Odds ratio among intervention and control groups. (b) Relative risk and (c) Risk difference
showed varying efficacy (68–80%) of clonazepam in the intervention group compared to the control.[5,9,19-24]

There are limited clinical studies involving clonazepam for the management of JME; however, the clinical uses of clonazepam are promising and have a wide scope in epilepsy treatment.

**Conclusion**

The present meta-analysis provides a scientific basis for the clinical use of clonazepam in the management of JME. Clonazepam is effective in controlling myoclonic jerks but, at the same time, does not respond against generalized seizures. Clonazepam possesses significant ADME properties, but because of limited clinical support/research evidence for JME, still, the drug is not classified as universal in JME management. Compared to other AEDs, clonazepam is effective and well tolerated with minimal side effects in the case of JME.

**Study limitations**

One major limitation is the lack of clinical studies involving the intervention of clonazepam in the management of JME. We also reported studies with incomplete/lack of information on the control group. Another limitation of the current study is due to less number of clinical interventions that were reported in the case of clonazepam compared to other AEDs. There is a lack of universal and defined clinical methods to diagnose JME from epileptic syndrome subjects and populations.

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**Author contribution**

In the present study concepts, design, definition of intellectual content, literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review was carried out by Dr. Faisal Al-Otaibi.

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**Conflicts of interest**

There are no conflicts of interest.

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Supplementary Table 1: Odds ratio and CI among intervention and control groups. The result shown in the table are significant ($P<0.001$) with a high weightage

| Study                  | Intervention | Controls | Odds ratio | 95% CI       | z   | P       | Weight (%) |
|------------------------|--------------|----------|------------|--------------|-----|---------|------------|
|                        |              |          |            |              |     |         | Fixed      |
| Rafiei, 2009           | 6/15         | 3/16     | 2.889      | 0.568 to 14.682 |     |         | 16.24      |
| Panayiotopoulos et al., 1994 | 54/66        | 2/66     | 144.000    | 30.866 to 671.810 |     |         | 18.10      |
| Machado et al., 2013   | 22/38        | 2/17     | 10.313     | 2.062 to 51.584  |     |         | 16.56      |
| Prasad et al., 2003    | 16/35        | 1/35     | 28.632     | 3.517 to 233.080 |     |         | 9.76       |
| Dreifuss et al., 1975  | 4/10         | 3/10     | 1.556      | 0.244 to 9.913   |     |         | 12.52      |
| Fazio et al., 1975     | 24/32        | 5/25     | 12.000     | 3.386 to 42.525  |     |         | 26.82      |
| Total (fixed effects)  | 126/196      | 16/169   | 14.907     | 8.256 to 26.915  | 8.962| <0.001  | 100.00     |
| Total (random effects) | 126/196      | 16/169   | 11.652     | 3.216 to 42.215  | 3.739| <0.001  | 100.00     |
### Supplementary Table 2: Data table demonstrating relative risk and CI among intervention and control groups.

The result shown in the table are significant ($P<0.001$) with a high weightage.

| Study                      | Intervention | Controls | Relative risk | CI            | $z$  | $P$  | Weight (%) |
|----------------------------|--------------|----------|---------------|---------------|------|------|------------|
| 6/15          | 3/16         | 2.133    | 0.647 to 7.037| 16.45       |      |      |            |
| Panayiotopoulos et al., 1994| 54/66       | 2/66     | 27.000        | 6.864 to 106.20| 12.50|      |            |
| Machado et al., 2013            | 22/38       | 2/17     | 4.921         | 1.302 to 18.603| 13.26|      |            |
| Prasad et al., 2003            | 16/35       | 1/35     | 16.000        | 2.242 to 114.18| 6.07 |      |            |
| Dreifuss et al., 1975          | 4/10        | 3/10     | 1.333         | 0.396 to 4.487| 15.92|      |            |
| Fazio et al., 1975             | 24/32       | 5/25     | 3.750         | 1.670 to 8.422| 35.81|      |            |
| Total (fixed effects)          | 126/196     | 16/169   | 6.646         | 4.125 to 10.708| 7.783| <0.001| 100.00     |
| Total (random effects)         | 126/196     | 16/169   | 4.843         | 1.888 to 12.421| 3.283| <0.001| 100.00     |
Supplementary Table 3: Data table demonstrating risk difference and CI among intervention and control groups. The results shown in table are significant ($P<0.001$) with a high weightage.

| Study                  | Intervention | Controls | Risk Difference | 95% CI      | z  | P       | Weight (%) |
|------------------------|--------------|----------|-----------------|-------------|----|---------|------------|
|                        |              |          |                 |             |    |         | Fixed      | Random     |
| Rafiei, 2009           | 6/15         | 3/16     | 0.213           | -0.101 to 0.526 |    |         | 5.44       | 14.61      |
| Panayiotopoulos et al., 1994 | 54/66        | 2/66     | 0.788           | 0.686 to 0.890 |    |         | 51.44      | 20.22      |
| Machado et al., 2013   | 22/38        | 2/17     | 0.461           | 0.242 to 0.681 |    |         | 11.09      | 17.35      |
| Prasad et al., 2003    | 16/35        | 1/35     | 0.429           | 0.255 to 0.603 |    |         | 17.61      | 18.60      |
| Dreifuss et al., 1975  | 4/10         | 3/10     | 0.100           | -0.316 to 0.516 |    |         | 3.09       | 11.81      |
| Fazio et al., 1975     | 24/32        | 5/25     | 0.550           | 0.333 to 0.767 |    |         | 11.33      | 17.42      |
| Total (fixed effects)  | 126/196      | 16/169   | 0.548           | 0.471 to 0.625 | 13.995 | <0.001  | 100.00     | 100.00     |
| Total (random effects) | 126/196      | 16/169   | 0.458           | 0.243 to 0.673 | 4.174  | <0.001  | 100.00     | 100.00     |