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REVIEW ARTICLE

The Delayed-Release Combination of Doxylamine and Pyridoxine (Diclegis®/Diclectin®) for the Treatment of Nausea and Vomiting of Pregnancy

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Abstract Nausea and vomiting of pregnancy (NVP) affects up to 85 % of all pregnancies. Effective treatment can greatly improve a woman's quality of life, reduce the risk for maternal and fetal complications, and reduce healthcare costs. Unfortunately, many women receive either no pharmacological treatment or are recommended therapies for which fetal safety and efficacy have not been established. First-line treatment of NVP, as recommended by several leading healthcare and professional organizations, is the combination of doxylamine and pyridoxine. This combination, formulated as a 10 mg/10 mg delayed-release tablet, was approved by the US Food and Drug Administration (FDA) for the treatment of NVP in April 2013 under the brand name Diclegis®, and has been on the Canadian market since 1979, currently under the brand name Diclectin®. The efficacy of Diclegis®/Diclectin® has been demonstrated in several clinical trials, and, more importantly, studies on more than 200,000 women exposed to doxylamine and pyridoxine in the first trimester of pregnancy have demonstrated no increased fetal risk for congenital malformations and other adverse pregnancy outcomes. The present review aims to present the scientific evidence on the effectiveness and fetal safety of Diclegis®/Diclectin® for the treatment of NVP to justify its use as first-line treatment for NVP.

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1 Introduction

1.1 Clinical Presentation of Nausea and Vomiting of Pregnancy (NVP)

Nausea and vomiting of pregnancy (NVP), the most prevalent medical condition in pregnancy, affects up to 85 % of pregnant women. The commonly used term "morning sickness" is misleading as the symptoms of NVP can occur throughout the day and/or night. In a study involving 160 pregnant women, 74 % reported NVP symptoms, of whom, only 1.8 % experienced "morning sickness", whereas, 80 % experienced NVP throughout the day [1]. Symptoms of NVP include nausea, gagging, retching and/or vomiting. Typically, symptoms of NVP appear between 4 and 9 weeks of pregnancy, and are usually most severe between 7 and 12 weeks of pregnancy. For the majority of pregnant women, symptoms subside between 12 and 16 weeks of pregnancy; however, for up to 15 % of women, symptoms continue up to 20 weeks gestation, and less than 10 % of women suffer throughout their entire pregnancy [2, 3].

The severity of NVP can range from mild to severe. The most severe form of NVP is known as hyperemesis gravidarum (HG), which affects up to 0.3–2 % of pregnant women. HG typically requires hospitalization because of severe and persistent nausea and vomiting, weight loss greater than 5 % of pre-pregnancy weight, dehydration, electrolyte imbalances, and nutritional deficiencies [2–5]. Women who have had NVP in a previous pregnancy are more likely to have recurrence of NVP in subsequent

pregnancies with the severity of NVP typically increasing in subsequent pregnancies. A 2004 study demonstrated that initiating any antiemetic treatment prior to or on first day of symptoms effectively lessened the severity of symptoms and reduced the recurrence of HG in women who experienced NVP in a previous pregnancy [6]. Because of the high recurrence rate of NVP symptoms (75–85 %), it is important for women to receive early treatment to reduce the severity of symptoms, with the aim of preventing the need for hospitalization and improving quality of life [3].

1.2 Etiology of NVP

Although there are several theories, the etiology of NVP is thought to be multi-factorial and still remains unknown. This contributes to the difficulty in management of the condition, as no single theory has been shown to be applicable to all women [2–4, 7]. The most common theory is that hormonal changes during the first trimester of pregnancy, specifically human chorionic gonadotropin hormone (hCG), estrogen and progesterone, contribute to NVP. Women with molar and multiple pregnancies have higher hCG levels and, often, worse symptoms of NVP [2, 8]. Other hormonal imbalances, such as thyroid disorders, are thought to be associated with NVP as well. For example, women with hyperthyroidism have been found to be more prone to experience more severe symptoms of NVP [4, 8, 9]. Nausea during the first trimester is also associated with gastric slow wave dysrhythmias which correlate closely with symptomatology [10]. It has been shown that the intensity of nausea is significantly greater in pregnant women with gastric dysrhythmias than in those with normal electrogastrographic patterns [8, 11, 12]. Research also shows that women with either pre-existing gastrointestinal (GI) conditions or untreated GI conditions, such as constipation, acid reflux and heartburn, ulcerative colitis, Crohn's disease, Celiac disease or irritable bowel syndrome, are susceptible to more intense symptoms of NVP [11–13]. Many studies, including a meta-analysis, have shown an association between *Helicobacter pylori* infection and HG and/or severe NVP [14–16].

Additional factors such as underlying psychiatric conditions, liver abnormalities, elevated cytokine levels, vitamin deficiencies (vitamin B_6, B_1, and K), as well as the evolutionary adaptation have been proposed as part of the etiology for NVP [4, 9, 17]. Other studies have demonstrated evidence for genetic contributions for NVP susceptibility, which include familial recurrence, carrying a female fetus, monozygotic twin pair correlation, and previous history of HG [2, 18, 19].

1.3 Impact of NVP

Many studies have demonstrated that NVP can negatively affect women's quality of life and their overall well-being [3, 20, 21]. Feelings of frustration, helplessness, resentfulness, and depression are common, experienced by 55 % of women suffering from NVP [12, 22]. These feelings, in turn, negatively influence a woman's social life and family, with approximately half of women reporting adverse effects on their marital relationships due to NVP [22]. In fact, because of the substantial impact of NVP, some women have electively terminated their pregnancy. In a study of 3,201 pregnant women experiencing NVP, 108 terminated their pregnancy because of NVP, and an additional 413 women considered termination [23]. In addition to the aforementioned physical and emotional consequences, NVP also has a significant financial impact on both individuals and society [24, 25]. A recently published study estimated the 2012 total economic burden from NVP in the USA to be US$1,778,473,782—60 % in direct costs and 40 % in indirect costs—with the average cost of US$1,827 to manage one woman with NVP [25].

On the other hand, several studies have suggested that the presence of NVP is a predictor of favorable pregnancy outcome. In fact, this condition may have a protective effect on pregnancy, as studies have shown lower rates of miscarriages, stillbirths, preterm births, and birth defects [3, 9, 26]. Furthermore, a study in 121 mother–child pairs found that women who experienced NVP gave birth to infants with higher neurodevelopment scores compared with women without NVP [27]. However, for women with insufficiently managed severe NVP or HG, there is an increased risk for adverse pregnancy outcomes such as small for gestational age, low birth weight, preterm delivery and low 5-min Apgar score [28–30].

1.4 Management of NVP

Women with mild symptoms may find lifestyle and dietary modifications to be sufficient to manage NVP symptoms [31]. Additionally, non-pharmacological interventions such as acupressure bands, acupuncture or ginger root powder capsules may be used; however, studies have demonstrated that the efficacy and safety vary [31, 32].

A large number of antiemetics have been proven effective for the treatment of nausea and vomiting associated with conditions such as chemotherapy-induced nausea and vomiting, motion sickness, GI conditions or cyclic vomiting [33]. However, their use in pregnancy is marred by lack of sufficient data on effectiveness and fetal safety [34]. The only drug approved and indicated for the treatment of NVP is the delayed-release formulation of 10 mg doxylamine succinate and 10 mg pyridoxine hydrochloride (HCl), as it has been shown to be both effective and safe [35–39]. This combination is currently available as Diclegis® in the USA and Diclectin® in Canada.

Several leading professional organizations, such as the American College of Obstetricians and Gynecologists

(ACOG) [40], the American Professors of Gynecology and Obstetrics [3], and the Society of Obstetricians and Gynecologists of Canada [41], and also teratogen information services, such as the Motherisk Program and MothertoBaby (formerly known as Organization of Teratogen Information Services) [42], recommend Diclegis®/Diclectin® as first-line therapy for the treatment of NVP. This recommendation is based on the extensive fetal safety and efficacy data available for this medication. The purpose of this review is to present the scientific evidence on the pharmacology, effectiveness, and fetal safety of Diclegis®/Diclectin® as first-line treatment for NVP.

2 History of Doxylamine/Pyridoxine

This combination was first introduced in the USA as Bendectin® in 1956. Initially, Bendectin® was formulated as a delayed-release combination of 10 mg doxylamine succinate, 10 mg pyridoxine, and 10 mg dicyclomine HCl [35, 43]. However, in 1976, an eight-way study of doxylamine, pyridoxine HCl, and dicyclomine showed that dicyclomine had no independent antiemetic effect, and therefore, Bendectin® was reformulated to contain 10 mg doxylamine succinate and 10 mg pyridoxine HCl [44–46]. Bendectin® was the drug of choice for NVP in the USA and other parts of the world under different trade names: Diclectin® in Canada, Debendox® in the UK and Australia, Lenotan® in Germany and Switzerland as well as in other countries of Europe, South America and Africa. It was widely prescribed and used by over 33 million women worldwide between 1956 and 1983 [43]. However, in 1983, Bendectin® was voluntarily removed from the American market by the manufacturer, Merrell Dow Pharmaceuticals, because of litigations and false allegations about teratogenic effects. The International Federation of Gynecology and Obstetrics described the removal of Bendectin® as "the worst example in history of women being denied medication without a cause" [22]. At that time, Bendectin® was the most studied drug in pregnancy, as a large number of cohort and case–control studies, as well as two separate meta-analyses, had demonstrated that it did not increase the risk of birth defects [36, 37, 45]. Committees assembled by both the FDA and Health Canada supported these findings, stating that the drug combination of doxylamine succinate and pyridoxine HCl does not increase malformation risk [47, 48].

After the removal of Bendectin® from the American market, the rates of hospitalization for severe NVP more than doubled in American women [45, 49]. With continuous use of Diclectin® in Canada, however, the rates of hospitalization for NVP in Canada have been shown to be lower than in the USA [47, 49]. This powerful evidence produced ecological, population-based proof for the therapeutic effectiveness of Bendectin® [49]. It also painfully demonstrated the risks of denying women safe and effective pharmacotherapy during pregnancy. Even though the combination of doxylamine and pyridoxine was not commercially available in the USA, it has been recommended by the ACOG as first-line therapy for the treatment of NVP since 2004 [40]. Unfortunately, these recommendations have led to the use of over-the-counter (OTC) preparations containing doxylamine, which are not equivalent in efficacy or fetal safety to the delayed-release formulation of Diclegis®, as they contain more than 10 mg of doxylamine as well as other active and inactive ingredients. Similarly, compounding pharmacies have combined doxylamine and pyridoxine in an attempt to offer pregnant women with NVP a suitable treatment option; however, to our knowledge, the safety and efficacy of these preparations have not been studied or approved by any regulatory agency. Combining 25 mg or 12.5 (if the tablet is cut) of doxylamine + 10 mg pyridoxine is not equivalent in efficacy to a delayed-release formulation combining 10 mg doxylamine + 10 mg pyridoxine. Furthermore, the concerns regarding safety include the following facts that (1) women have to ensure that they purchase the correct OTC medication that only includes doxylamine as the active ingredient, (2) women have to ensure they cut the 25 mg tablet in half, (3) various excipients may be present in the OTC forms of doxylamine that may have not been studied for fetal safety, and (4) no other doxylamine-containing product has a Pregnancy Category A rating by the FDA.

3 Composition of Diclegis®/Diclectin®

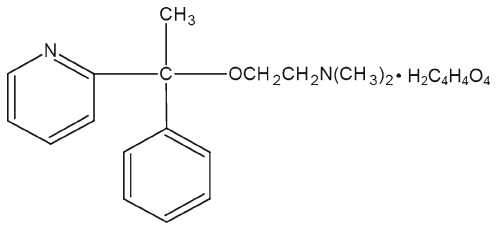
Diclegis®/Diclectin® are round, white, film-coated, delayed-release tablets imprinted with the pink image of a pregnant woman to indicate that the tablet is for pregnant women [50, 51]. Diclegis®/Diclectin® is a combination of 10 mg doxylamine succinate (an antihistamine) and 10 mg pyridoxine HCl (vitamin B_6). Doxylamine succinate and pyridoxine HCl provide independent anti-nauseant and antiemetic activity [52–54]. The unique characteristic of Diclegis®/Diclectin® tablets that allows it to control NVP symptoms is the delayed-release action, making it critical to use on a strict schedule, and not on an as-needed basis [55]. The enteric coating ensures that the active ingredients are released in a pH-dependent manner along the gut and small intestine to provide sustained antiemetic and anti-nauseant relief. In contrast, OTC preparations containing doxylamine are not formulated to be delayed-release, and hence, would not be able to effectively control NVP symptoms in the same manner as Diclegis®/Diclectin®. The standard recommended dose of Diclegis®/Diclectin®

is typically up to four tablets daily: two tablets at bedtime, one in the morning, and one in the mid-afternoon. This delayed-release formulation permits the antiemetic action to occur 4–6 h after ingestion; therefore, the bedtime dose would be effective in the early morning, the morning dose would be effective in the afternoon and the mid-afternoon dose would be effective in the evening, providing 24 h control of NVP symptoms [50, 51].

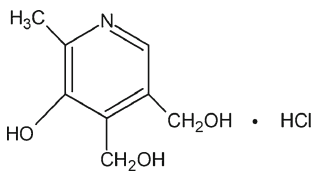
3.1 Doxylamine Succinate

Doxylamine succinate (Fig. 1a) is structurally related to histamine and strongly antagonizes histamine's effects on histamine 1 (H_1) receptor sites; as a result, it possesses sedative effects. It is a member of the ethanolamine class of first-generation antihistamines. As with other members of this group of drugs, doxylamine possesses substantial antimuscarinic activity with low incidence of GI adverse effects [56]. As with any other H_1 blocker, doxylamine may exhibit anticholinergic effects if taken in large doses [54, 56].

Doxylamine is well absorbed from the GI tract, with peak plasma concentrations achieved within 2–3 h, and the therapeutic effects usually persist for 4–6 h. Doxylamine is biotransformed in the liver by *N*-dealkylation to its principal metabolites *N*-desmethyl and *N*, *N*-didesmethyldoxylamine, which are excreted by the kidney [57]. Importantly, the delayed-release formulation of Diclegis®/Diclectin® tablets has different pharmacokinetics, which will be discussed below.



a Doxylamine succinate



b Pyridoxine hydrochloride

Fig. 1 Chemical structure of Diclegis®/Diclectin® [10 mg doxylamine succinate/10 mg pyridoxine hydrochloride (HCl)]. **a** Doxylamine succinate is classified as an antihistamine. The chemical name for doxylamine succinate is ethanamine, *N*,*N*-dimethyl-2-[1-phenyl-1-(2-pyridinyl)ethoxy]-butanedioate (1:1) 2-[α-[2-(dimethylamino)ethoxy]-α-methylbenzyl] pyridine succinate (1:1). The empirical formula is $C_{17}H_{22}N_2O \cdot C_4H_6O_4$ and the molecular mass is 388.46 g/mol. It is very soluble in water and alcohol, readily soluble in chloroform, and slightly soluble in ether and benzene. **b** Pyridoxine HCl is vitamin B_6. Its chemical name is 5-hydroxy-6-methyl-3,4-pyridine dimethanol hydrochloride. The empirical formula $C_8H_{11}NO_3 \cdot HCl$ and molecular mass is 205.64 g/mol. Pyridoxine HCl is readily soluble in water, slightly soluble in alcohol, and insoluble in ether

3.2 Pyridoxine Hydrochloride

Pyridoxine HCl (Fig. 1b) is the usual form of vitamin B_6 included in pharmaceutical products. Vitamin B_6 is a collective name for pyridoxine, pyridoxal, and pyridoxamine, which are related natural compounds with similar biological properties [58].

Pyridoxine is readily absorbed from the GI tract, mainly in the jejunum. The drug is primarily metabolized in the liver to its four active metabolites pyridoxal, pyridoxal-5-phosphate (PLP), pyridoxamine, and pyridoxamine-5-phosphate. Following phosphorylation, its main metabolite, PLP, is released into the circulation and is highly protein bound. PLP is a cofactor in over 160 enzyme activities involved in a number of metabolic processes of amino acids, nucleic acids, unsaturated fatty acids, carbohydrates, glycogen, neurotransmitters, and porphyrin. The major metabolite 4-pyridoxic acid is inactive, and is excreted by the kidney [58–61].

4 Pharmacokinetics of Diclegis®/Diclectin®

The first study on the pharmacokinetics of Diclectin® was published in 2009, almost 50 years after the invention of the delayed-release combination of doxylamine/pyridoxine (Bendectin®) [62]. The purpose of this study was to confirm the delayed-release properties of Diclectin®. This randomized, crossover, open-label study compared the pharmacokinetics of the parent drugs, doxylamine succinate and pyridoxine HCl, and certain metabolites, pyridoxal and PLP, after oral administration of Diclectin® tablets (2 × 10 mg/10 mg) to a reference combination of doxylamine succinate and pyridoxine HCl oral solution (20 mL × 10 mg/10 mL). The study included 18 healthy, non-pregnant women of childbearing age under fasting conditions. Diclectin® exhibited similar bioavailability to the oral solution. Mean peak plasma concentration (C_{max}) levels were similar for both doxylamine and pyridoxine after administration of Diclectin® (90.4 ± 13.1 vs. 98.7 ± 18.1 ng/mL) and the oral solution (50.7 ± 31.0 vs. 96.5 ± 46.7 ng/mL). In contrast, mean time to peak plasma level (T_{max}), reflecting the rate of absorption, was shown to be three times longer for doxylamine (6.10 ± 1.77 vs. 2.04 ± 0.85 h), six times longer for pyridoxine (3.81 ± 1.20 vs. 0.618 ± 0.179 h), four times longer for pyridoxal (4.84 ± 1.44 vs. 1.15 ± 0.26 h), and

six times longer for total pyridoxine after administration of Diclectin® compared with the oral solution ($P < 0.0001$). Mean T_{max} values for PLP after administration of Diclectin® and the oral solution were similar (8.59 ± 2.77 vs. 7.64 ± 3.88 h). Results from this study verified the delayed-release property of Diclectin®.

Another single-center, open-label study including 18 non-pregnant, non-lactating, premenopausal women was conducted to determine the pharmacokinetics of doxylamine succinate and pyridoxine HCl after administration of a single dose of Diclectin® (2 × 10 mg/10 mg) under fasting conditions [63]. The mean plasma–concentration profiles of doxylamine succinate and PLP demonstrated large variability among participants; furthermore, twofold variability was observed in the systemic exposure to doxylamine and 6.5-fold for PLP based on the mean area under the curve ($AUC_{0\rightarrow\infty}$). In this study, for doxylamine, the mean elimination half-life ($T_{½}$) was calculated to be 11.7 h, and mean C_{max} was 90 ng/mL. For PLP, mean $T_{½}$ was 56 h, and mean C_{max} was 42.9 ng/mL. This study also calculated the bioavailability of pyridoxine to be 100 % [63].

A recent study determined the effect of sex on the pharmacokinetics and bioequivalence (BE) of Diclectin® [64]. This single-center, reference-replicate study calculated the pharmacokinetic parameters from 1 h pre-dose until 72 h post-dose in healthy males ($n = 12$) and non-pregnant females ($n = 12$) after oral administration of two tablets. After 21 days, drug dosing and blood sampling was re-conducted as stated above. Results from this study found that females had significantly larger AUC_{0-t} for both doxylamine ($P \leq 0.05$) and pyridoxine ($P \leq 0.05$) compared with males. They also had higher C_{max} for doxylamine ($P \leq 0.05$). BE testing did not show BE between males and females. The authors concluded that these results may have implications for future BE studies using doxylamine/pyridoxine, and that this drug, for use exclusively in women, should be studied in women and not in men [64].

The only study on the pharmacokinetics of doxylamine/pyridoxine delayed-release combination in pregnant women was recently published [65]. This study combined data from two published studies to compare the pharmacokinetics of Diclectin® in 18 non-pregnant women of childbearing age with 50 women in the first trimester of pregnancy treated with Diclectin® for NVP [39, 62]. The two sets of data allowed comparison of steady-state trough concentrations of doxylamine and of PLP. No differences in the apparent clearance (CL) of doxylamine were found between women in their first trimester of pregnancy and non-pregnant women on day 4 (median = 196.7 vs. 249.5 mL/h/kg, respectively, $P = 0.065$), day 8 (median = 248.4 vs. 249.5 mL/h/kg, respectively, $P = 0.82$), and day 15 (median = 200.9 vs. 249.5 mL/h/kg, respectively, $P = 0.55$). There was no difference in the apparent CL of PLP on day 15 (median = 342.3 vs. 314.7 mL/h/kg, respectively, $P = 0.92$). The results demonstrated that there was no pregnancy-induced effect in the apparent CL of both doxylamine and PLP in women during the first trimester of pregnancy despite the existence of NVP. Their data also indicate that the trough steady-state concentrations in women suffering from mild and moderate forms of NVP are not different from those achieved among non-pregnant controls [39, 62, 65].

Table 1 Studies on the pharmacokinetics and bioavailability of the delayed-release combination of doxylamine/pyridoxine (Diclegis®/Diclectin®)

Author and year	Study objective	Study subjects	Main results	Ref
Nulman et al., 2009	Pharmacokinetics of Diclectin®	18 non-pregnant females	Doxylamine C_{max} threefold longer with Diclectin® than with oral solution	[62]
Gill et al., 2011	Systemic bioavailability and pharmacokinetics of Diclectin® after single dose under fasting conditions	18 non-pregnant females	The systemic bioavailability of Diclectin® appears to be around 100 %	[63]
Koren et al., 2013	Effect of sex on pharmacokinetics and bioequivalence of Diclectin®	24 (12 males/12 females, non-pregnant)	Bioequivalence testing did not demonstrate bioequivalence betwen males and females. Females have significantly larger systemic exposure to both components of Diclectin® than males	[64]
Matok et al., 2013	Comparing the pharmacokinetics of Diclectin® in non-pregnant females and in the first trimester of pregnancy	50 females in first trimester of pregnancy compared with 18 non-pregnant females	In the first trimester of pregnancy, the pharmacokinetics of Diclectin® are similar to those of non-pregnant females	[65]
Rowland et al., 1989	Pharmacokinetics of doxylamine in pregnant primates	Primates	No pregnancy-induced changes in pharmacokinetics	[66]

C_{max} peak plasma concentration

A summary of all pharmacokinetic studies on Diclectin® is provided in Table 1.

The results obtained from these recent pharmacokinetic studies from Diclectin® in pregnant women confirm the results of a doxylamine pharmacokinetic study in pregnant primates from the late 1980s [66]. This study examined differences in the pharmacokinetics of doxylamine among baboons, cynomolgus monkeys and rhesus monkeys, and evaluated whether pregnancy had any effect on its pharmacokinetics when compared with non-pregnant rhesus monkeys. The study also evaluated whether multiple dosing of doxylamine alters its pharmacokinetics. The monkeys were administered a dose of 7 mg/kg/day (ten times the maximum human dosage) from days 22 to 50 of pregnancy. The results showed that there were no significant differences in pharmacokinetics among the three groups, and from those of non-pregnant rhesus monkeys. The pharmacokinetics of doxylamine after multiple dosing (day 50) was shown to be similar to the pharmacokinetics after single-dose administration on day 22. The study concluded that there were no pregnancy-induced changes in the pharmacokinetics of the doxylamine/pyridoxine combination [66].

These observations are of substantial clinical importance, indicating that during the first trimester of pregnancy, the major changes in the volume of distribution, protein binding and CL rate seen in later pregnancy for many other drugs are not found to occur with doxylamine. Although care should be exercised to avoid over-interpreting data from doxylamine compared with other drugs, these findings suggest that pharmacokinetic studies in fecund, non-pregnant women may reflect doxylamine disposition characteristics during the first trimester of pregnancy.

5 Clinical Effectiveness of the Delayed-Release Combination of Doxylamine/Pyridoxine

The clinical effectiveness of the delayed-release combination of doxylamine and pyridoxine has been documented in several randomized, controlled trials as well as in open post-marketing studies using Bendectin®, Debendox®, and Diclectin®. Additionally, several placebo-controlled clinical trials have been published, the results of which will be reviewed here.

The findings of a double-blind, placebo-controlled trial of Bendectin® (10 mg doxylamine, 10 mg pyridoxine, and 10 mg dicyclomine) were reported in 1959 [67]. The study groups consisted of 109 patients, 52 randomized to receive Bendectin® and 57 to placebo, showing a favorable response to the active drug preparation of 94 % compared with only 65 % for placebo ($P < 0.001$). Of the patients who received Bendectin®, 23 (44 %) experienced complete relief of nausea.

Another double-blind, placebo-controlled trial found that in 70.7 % ($n = 41$) of patients who received Debendox® (10 mg doxylamine, 10 mg pyridoxine, and 10 mg dicyclomine), improvement in NVP severity was noted, compared with 55 % ($n = 40$) in those receiving placebo ($P < 0.05$) [68].

In a subsequent randomized, double-blind trial, the same active drug combination Debendox® (10 mg doxylamine, 10 mg pyridoxine, and 10 mg dicyclomine) with 10 mg of extra pyridoxine, or placebo along with 10 mg of pyridoxine, was given to 56 pregnant women suffering from NVP during the first 10 weeks of pregnancy, in a crossover design [69]. Differences in nausea severity were statistically significant ($P < 0.001$) when treatment with placebo in the first week was changed to the active drug in the second week. Similarly, significant superiority for the active treatment was noted with regard to the severity of retching ($P < 0.05$) and vomiting ($P < 0.02$).

Results from two placebo-controlled studies on the efficacy of all individual components of Bendectin® were evaluated by the manufacturer of the drug, Merrell Dow Pharmaceuticals. These results are also summarized in a review known as the Drug Effectiveness Study Implementation process, which was conducted by the National Academy of Sciences and the FDA [46]. The first study compared the efficacy of doxylamine plus dicyclomine, doxylamine, dicyclomine and placebo for NVP treatment in 716 patients. These results demonstrated that doxylamine plus dicyclomine was more effective for NVP treatment than placebo, a finding that was attributed to doxylamine since dicyclomine was not significantly more effective than placebo. The other study evaluated the efficiency of all components of Bendectin®, including pyridoxine alone and in various possible combinations, compared with placebo in more than 2,300 women with NVP [46]. The results confirmed that the efficacy of Bendectin® was greater than that of placebo but showed no antiemetic contribution from dicyclomine. Doxylamine was the major component that demonstrated clear effectiveness in NVP treatment, while pyridoxine had a clear effect on nausea but probably not vomiting [46, 70]. Following these studies, dicyclomine was removed from the formulation, and Bendectin® continued to be manufactured as a combination of doxylamine and pyridoxine only.

One of the limitations of all of the previous studies was their short duration, which did not permit evaluation of long-term effectiveness, which is important in view of the possibility of reduced patient compliance due to potential adverse effects such as sedation. A study was conducted in 149 women being counseled by the Motherisk NVP program in Toronto, Canada [70]. Participants were advised to take two Diclectin® tablets at bedtime; if NVP symptoms became apparent in the afternoon despite the previous

evening dose, they were advised to take an additional tablet in the morning. A fourth tablet was taken at noon by participants whose NVP symptoms occurred in the late afternoon or evening. The first interview was conducted after the onset of symptoms, at six to eight weeks gestation, and the second evaluation was at 20 weeks. During the first interview of 106 patients, 71 % reported an improvement in their NVP symptoms due to Diclectin® use, 23 % did not report improvement and 1 % reported worsening of their symptoms. By 20 weeks gestation, an additional 25 of the original cohort of patients started Diclectin® therapy; 21 (84 %) reported improvement, 3 (12 %) reported no change, and 1 (4 %) experienced a worsening of symptoms. These results are very similar to those reported in the double-blind trial above [69], suggesting that, in the clinical setting, Diclectin® does not lose efficacy over time. It also showed that of 11 women who increased their dosage before 20 weeks, all reported NVP symptom improvement [70].

A quantitative and qualitative overview of observational, controlled, and randomized, controlled trials for drug effectiveness for NVP was conducted. The authors analyzed the safety and efficacy of NVP treatments and concluded that antihistamines, including Diclectin® and Bendectin®, are both safe and effective for NVP treatment [38].

Results from a randomized, double-blind, multicenter, placebo-controlled trial evaluating the effectiveness of the Diclectin® in the treatment of pregnant women (7–14 weeks gestation) suffering from NVP were published in 2010 [39]. Women were recruited in 2008–2009 from three university medical centers in the USA. Women received Diclectin® ($n = 131$) or placebo ($n = 125$) for 14 days. Symptoms of NVP were evaluated daily using the validated Pregnancy-Unique Quantification of Emesis (PUQE) scale [71]. Diclectin® therapy resulted in a significantly larger improvement in symptoms of NVP compared with placebo ($P = 0.006$) [39]. After the trial, 64 women (48.9 %) receiving Diclectin® asked to continue compassionate use of their medication, as compared with 41 placebo-treated women (32.8 %) ($P = 0.009$). The use of Diclectin® was not associated with an increased rate of any adverse events as compared with the placebo group [39].

Very strong evidence supporting the effectiveness of this delayed-release combination is provided by population-based studies conducted in the USA and Canada [45, 49]. The withdrawal of Bendectin® from the American and Canadian markets was temporally related to a two- to threefold increase in the rates of hospitalization of women for NVP [45, 49]. These data suggest that the doxylamine/pyridoxine combination is not only capable of eradicating mild and moderate forms of NVP, but also of preventing severe cases. New data from Neutel reiterate these findings: the increased use of Diclectin® by Canadian women during the 1990s has been associated with a reduction in the hospitalization rate for severe NVP [70, 72]. This information provides further convincing evidence for the strong impact of Diclectin® on the health of thousands of pregnant women in Canada. A summary of the studies on the clinical effectiveness of the delayed-release combination of doxylamine/pyridoxine is presented in Table 2.

6 Optimal NVP Treatment Using Diclegis®/Diclectin®

Optimal treatment is especially important in cases of severe NVP and HG where women reported that under-managed NVP symptoms led them to terminate otherwise wanted pregnancies [23, 33]. Effective treatment is also important in less severe cases where inadequate symptom control often leads to poor quality of life, as well as time lost from work, lowered productivity and decreased ability to function [25, 73]. To ensure optimal efficacy, Diclegis®/Diclectin® should not be used on an as-needed basis [55]. It can be used as soon as NVP symptoms appear, and in any trimester of pregnancy [55]. A gradual dose tapering is recommended rather than sudden discontinuation to avoid return of NVP symptoms [50]. A summary of studies on efficacy and characteristics of optimal treatment using Diclegis®/Diclectin® is presented in Table 3.

Because of the unique pharmacokinetic profile of this drug, optimal dosing and timely use are very important in appropriate control of NVP symptoms. The rates of suboptimal use and effect of optimal dosing of Diclectin® as a measure of effectiveness of NVP treatment was evaluated [74]. Patients were recruited from the Motherisk NVP Helpline, assessed for NVP severity using PUQE scores, and their Diclectin® doses were subsequently increased according to body weight and individual symptoms. Sixty-eight women were enrolled and completed the study. Most of the women (50/68) were receiving suboptimal doses of Diclectin® despite their moderate to severe NVP, defined by the PUQE scale. Following a correction of the dose to four tablets a day, there was a significant decrease in length of nausea (from 4 to 3 h, $P < 0.001$), frequency of vomiting (from mean 1.6 to 1.3 a day, $P = 0.02$), and overall PUQE score (from mean 7.5 to 6.1, $P < 0.001$). This study demonstrated that Diclectin® should be dosed according to body weight and severity of symptoms [74].

Another observational, prospective study showed the improved effectiveness of appropriate dosing of Diclectin® using more than four tablets per day based on the severity of NVP symptoms and adjustment for body weight. No increase in adverse events or adverse pregnancy outcomes for the higher than standard dose of Diclectin® were observed [75].

In a secondary a priori analysis of data from the multicenter, double-blind, randomized, controlled trial of Diclectin® versus placebo for the treatment of NVP, the

Table 2 Summary of the studies on clinical efficacy of the delayed-release combination of doxylamine/pyridoxine

Author and year	Drug studied	Number of subjects	Study type	Main results	Ref
Geiger et al., 1959	Bendectin®	109 (52 Bendectin®; 57 placebo)	Double-blind, placebo-controlled	Improvement of NVP in 94 % in exposed group/65 % in placebo ($P < 0.001$)	[67]
McGuinness and Binns, 1971	Debendox®	81 (41 Debendox®; 40 placebo)	Double-blind, placebo-controlled	Improvement of NVP in 70.7 % in exposed group/55 % in placebo ($P < 0.05$)	[68]
Wheatley et al., 1977	Debendox® + 10 mg pyridoxine/ placebo + 10 mg pyridoxine	56	Crossover, double-blind, placebo-controlled	Improvement in nausea ($P < 0.001$), severity of retching ($P < 0.05$), and vomiting ($P < 0.02$)	[69]
DESI, Bendectin 4-way study, 1972	Bendectin®	716 (doxylamine/ dicyclomine)	Double-blind, placebo-controlled	Doxylamine and dicyclomine more effective than placebo	[46, 70]
DESI, Bendectin 8-way study, 1975	Bendectin®	2300 (doxylamine/ dicyclomine/ pyridoxine)	Double-blind, placebo-controlled (various combinations of the ingredients with placebo)	Doxylamine most effective, dicyclomine no effect, pyridoxine effective for nausea but not vomiting	[46, 70]
Bishai et al., 2000	Diclectin®	149 (long-term effectiveness)	Observational	Improvement in NVP 71 % in first 6–10 gw, 84 % in 20 gw	[70]
Magee et al., 2002	Antiemetics including antihistamines/ Diclectin®/ Bendectin®	24 controlled studies on safety of antihistamines; 7 controlled studies on efficacy	Quantitative and qualitative overview of observational, controlled, and randomized, controlled trials	Antihistamines, Diclectin® and Bendectin® safe and effective	[38]
Koren et al., 2010	Diclectin®	256 (131 Diclectin®, 125 placebo)	Randomized, double-blind, multicenter, placebo-controlled	Improvement of NVP symptoms in Diclectin® group ($P < 0.006$) compared to placebo group	[39]
Kutcher et al., 2003	Bendectin®	Ecological analyses	Epidemiological multicenter USA data (birth defects, sales, hospitalization)	No teratogenic effect of Bendectin®, twofold increase in hospitalization for women with NVP with decreased sales of Bendectin	[45]
Neutel and Johansen, 1995	Bendectin®/ Diclectin®	Epidemiological analysis	Epidemiological data	Two- to threefold increase of hospitalizations rate after removal of Bendectin®	[49]

NVP nausea and vomiting of pregnancy, *gw* gestational weeks

authors aimed to identify the determinants of adherence to Diclectin® in 258 patients with NVP. There were no differences in adherence rates according to ethnicity, race, or the presence of adverse events [76]. Gravidity, average number of prescribed tablets per day, site of enrollment, and change in NVP severity measured by the PUQE score were associated with adherence. In the multivariable analysis, average number of tablets per day, change in PUQE score, number of treatment days, and site of enrollment were significantly predictive of adherence, with the former being negatively correlated. The authors concluded that the adherence to Diclectin® is dependent on the number of tablets prescribed per day, and treatment duration and effectiveness [76].

A recent prospective, randomized, controlled trial compared the effectiveness of the preemptive use of Diclectin® in women who had experienced severe NVP and/or HG in their previous pregnancy to women with a similar previous experience who received Diclectin® only on the first sign of nausea, in addition to both groups receiving standardized counseling [77]. A total of 30 women were randomized into the preemptive group (initiation of Diclectin® before symptoms began) and 29 into the control arm (initiation of Diclectin® at the first sign of NVP). The initial dose of Diclectin® was two tablets at bedtime and was gradually adjusted to NVP severity. Preemptive therapy conferred a significant reduction in HG as compared with the previous pregnancy ($P = 0.047$). In the preemptive arm, there were 2.5-fold fewer cases of moderate-severe cases of NVP than those in the control group (15.4 vs. 39.13 %) in the first 3 weeks of NVP

Table 3 Summary of the studies on efficacy and characteristics of optimal treatment with the delayed-release combination of doxylamine/pyridoxine (Diclectin®)

Author and year	Drug studied	Subjects	Study type	Main results	Ref
Boskovic et al., 2003	Diclectin®	68 females (suboptimally treated with 2 tablets/day instead of 4 tablets/day)	Observational, prospective study (optimal dosing by body weight and severity of symptoms)	Significant improvement of nausea ($P < 0.001$), frequency of vomiting ($P = 0.02$), and PUQE scores ($P < 0.001$) with optimal dosing	[74]
Atanackovic et al., 2001	Diclectin®	225 females ($n = 123$ used recommended dose 4 tablets/day; $n = 102$ used more than recommended dose > 4 tablets/day)	Observational, prospective study (adjustment by body weight and severity of symptoms)	Diclectin® can be given at doses higher than 4 tablets/day to normalize for body weight or optimize efficacy	[75]
Constantine et al., 2012	Diclectin®	258 females ($n = 131$ Diclectin® group, $n = 127$ placebo group)	Multicenter, double-blind, randomized, controlled trial of Diclectin® vs. placebo	Adherence to Diclectin® is dependent on the number of tablets prescribed per day, and treatment duration and effectiveness	[76]
Maltepe and Koren, 2013	Diclectin® preemptive treatment	59 females ($n = 30$ preemptive group: initiation of Diclectin® before symptoms began; $n = 29$ control group: initiation of Diclectin® at the first sign of NVP)	Prospective, randomized, controlled trial	Preemptive therapy conferred a significant reduction in HG as compared with the previous pregnancy ($P = 0.047$). Significantly more women had their NVP resolved before giving birth (78.2 vs. 50 %) ($P < 0.002$) in preemptive group	[77]

HG hyperemesis gravidarum, *NVP* nausea and vomiting of pregnancy, *PUQE* Pregnancy-Unique Quantification of Emesis

($P = 0.05$). In the preemptive group, significantly more women had their NVP resolved before giving birth (78.2 vs. 50 %) ($P < 0.002$). These results, although preliminary, demonstrate that preemptive treatment with Diclectin® may be beneficial in decreasing the risk for severe forms of NVP [77].

Because the delayed-release combination was not available in the USA for 30 years, even though it was recommended as first-line treatment for NVP, a common practice in the USA became recommending separate OTC preparations of doxylamine and vitamin B_6 for NVP treatment. Although this therapy may, at most, yield short-lived relief of symptoms if women do not vomit the tablets before they are broken down and absorbed by the body, women will not benefit from the sustained therapeutic effect of the delayed-release form that has been demonstrated with the use of Diclegis®/Diclectin®. Moreover, doxylamine appears in numerous generic forms, under different names and dosages, and to our knowledge, not a single study has been published to demonstrate the safety and efficacy of these forms for treatment of NVP. It is important to note that the fetal safety of Diclegis®/Diclectin® has been well-established; however, other doxylamine-containing products have not received a FDA Pregnancy Category A rating and are not indicated for use in pregnancy. In order to ensure safe and effective therapy for NVP, Diclegis®/Diclectin® use should be first-line.

7 Fetal Safety of the Delayed-Release Combination of Doxylamine/Pyridoxine

As previously stated, the fetal safety of no other drug has been as extensively studied as the delayed-release combination of doxylamine and pyridoxine. Bendectin® was the most frequently prescribed antiemetic for the treatment of nausea and vomiting between 1956 and 1983, with an estimated 33 million exposures [47]. According to several studies, up to 40 % of women took the drug during their first trimester of pregnancy in the late 1970s and early 1980s. In 1969, allegations questioning Bendectin's safety were raised. While these were individual case reports that did not specify patients' past medical history, scores of similar cases were brought to court in the following years with claims of teratogenicity [43, 47]. As a result of escalating legal costs, the manufacturer decided to remove the drug from the market in 1983 [35, 78]. This decision was made despite the fact that a convincing body of scientific evidence had documented the safety of this product in pregnancy, including an expert panel convened by the FDA that unequivocally refuted the claims of teratogenicity [79].

Teratogenicity studies of the ingredients of Diclectin® in multiples of the maximal human dose (MHD) administered during the respective periods of organogenesis performed in rats (90× MHD), rabbits (up to 125× MHD), mice (up

Table 4 Summary of the studies on fetal safety of the delayed-release combination of doxylamine/pyridoxine

Author and year	Drug studied	Subjects	Study type	Main results	Ref
Einarson et al., 1988	Fetal safety of Bendectin®	Bendectin® exposed $n = 14{,}715$; $n = 115{,}544$ not exposed to Bendectin®	Meta-analysis, systematic analysis of data from 12 cohort and 5 case–control studies	Overall summary OR 1.01 (95 % CI 0.66–1.55). OR 0.95 (95 % CI 0.62–1.45) for cohort studies, and 1.27 (95 % CI 0.83–1.94) for case–control studies	[36]
McKeigue et al., 1994	Fetal safety of Bendectin®	Bendectin® exposed $n = 18{,}055$; controls $n = 150{,}714$, not exposed to Bendectin®	Meta-analysis, systematic analysis of data from 16 cohort and 11 case–control studies	RR for any malformation at birth in association with exposure to Bendectin® in the first trimester was 0.95 (95 % CI 0.88–1.04); pooled estimates of RR ranging from 0.81 for oral clefts to 1.11 for limb defects, with no differences between Bendectin® and the controls	[37]
Atanackovic et al., 2001	Fetal and maternal safety of Diclectin®	225 ($n = 123$ used recommended dose (1–4 tablets); $n = 102$ used more than recommended dose (5–12 tablets)	Observational, prospective study (adjustment by body weight and severity of symptoms)	Diclectin® given at doses higher than 4 tablets/day when calculated per kilogram of body weight did not affect either the incidence of maternal adverse effects or adverse pregnancy outcomes	[75]
Nulman et al., 2009	Safety information on neurodevelopment after exposure to Diclectin®	45 children born to mothers who had NVP and were exposed to Diclectin®, 47 children with mothers who had NVP but no Diclectin® exposure, and 29 children born to mothers without NVP	Observational, cohort study of mother–child pairs	Diclectin® does not adversely affect fetal brain development and can safely be used to treat NVP	[27]

CI confidence interval, *NVP* nausea and vomiting of pregnancy, *OR* odds ratio, *RR* relative risk

to 60× MHD), and monkeys (10–20× MHD) showed no consistent pattern of abnormalities following fetal exposure [35, 80, 81].

To address the question of potential teratogenicity of Bendectin® in humans, two separate meta-analyses were conducted which combined all controlled studies of pregnancy outcome following the use of this product during the first trimester. Both studies failed to show an overall increase in malformation rates, or in specific malformations. A systematic analysis of data from 12 cohort and five case–control studies totaling close to 200,000 patients calculated the overall summary odds ratio to be 1.01, indicating the absence of any increased risk, with a 95 % confidence interval (CI) of 0.66–1.55. When the two types of studies were separated according to their design, the summary odds ratio was 0.95 (95 % CI 0.62–1.45) for cohort studies, and 1.27 (95 % CI 0.83–1.94) for case–control studies [36].

A second meta-analysis was conducted combining data from 16 cohort and 11 case–control studies [37]. The pooled estimate of the relative risk for any malformation at birth in association with exposure to Bendectin® in the first trimester was 0.95 (95 % CI 0.88–1.04). Separate analyses for cardiac defects, limb defects, oral clefts, and genital tract malformations yielded pooled estimates of relative risk ranging from 0.81 for oral clefts to 1.11 for limb defects, with no differences between Bendectin® and the controls. As a group, these studies have shown no differences in the risk of birth defects between those infants whose mothers had taken Bendectin® during the first trimester of pregnancy and those who had not [37].

An observational, prospective study was conducted in Canada with the objective to determine the incidence of adverse maternal and fetal effects and pregnancy outcome in 225 women taking Diclectin® at the recommended (1–4 tablets) ($n = 123$) or higher than recommended (5–12 tablets) ($n = 102$) doses. The results showed that higher than standard dose of Diclectin®, when calculated per kilogram of body weight, did not affect either the incidence of maternal adverse effects or adverse pregnancy outcomes [75].

In addition to the safety data on malformations and other adverse pregnancy outcomes, Diclegis®/Diclectin® is one of the few drugs that has safety information on the neurodevelopment of children exposed in utero. An observational cohort study of mother–child pairs was conducted to

determine the effects of NVP and its treatment with Diclectin® on child neurodevelopment [27]. The mother–child pairs were ascertained through the Motherisk NVP Helpline. Three groups of children were studied: 45 born to mothers who had NVP and were exposed to Diclectin®, 47 with mothers who had NVP but no Diclectin® exposure, and 29 born to mothers without NVP. Information on pregnancy, birth and early child development was ascertained through phone calls to mothers during pregnancy and 6–9 months after childbirth. A comprehensive set of psychological tests was conducted in children aged 3–7 years, and mothers were assessed for IQ and socioeconomic status. The results showed that Diclectin® does not appear to adversely affect fetal brain development and can safely be used to treat NVP [27].

Table 4 presents the studies summarizing the fetal safety of the delayed-release combination of doxylamine/pyridoxine.

In 1989, a report on the safety of the drug combination of pyridoxine/doxylamine for use in the management of NVP was prepared by a panel of Canadian and American experts for the Special Advisory Committee on Reproductive Physiology to the Health Protection Branch of Health Canada (currently called the Health Products and Food Branch) [47]. These scientific experts concluded that "numerous studies in animals and in humans that have been reported in the scientific and medical literature demonstrate that Bendectin is not a teratogen…The safety of Bendectin®/Diclectin® in the management of nausea and vomiting of pregnancy has been established by its use in many thousands of pregnant women" [47].

The most reputable teratogen reference guides conclude that Diclegis®/Diclectin® is not associated with an increased risk for adverse pregnancy outcomes [82, 83]. Because of the extensive fetal safety data that exist, Diclegis® received a FDA Pregnancy Category A classification, indicating that adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy and there is no evidence of risk in later trimesters [79].

8 Conclusions

NVP remains a significant public health issue, and has negative physical, emotional, and financial consequences. Optimal treatment of this condition is warranted, and, to-date, the only approved medication indicated for the treatment of NVP is Diclegis®/Diclectin®. Furthermore, this drug has been recommended as first-line therapy for NVP treatment since the 1990s by leading professional organizations.

There is wide consensus that the Diclegis®/Diclectin® formulation is one of the best-studied drugs of all time for use in pregnancy, and that the great preponderance of evidence clearly confirms its documented effectiveness and safety profile. It is highly improbable that any other drug used for the treatment of NVP will ever be able to achieve the same degree of statistical power confirming the absence of a potential rare teratogenic effect. Similarly, individual components of doxylamine and pyridoxine available OTC are not able to control NVP symptoms as effectively as the delayed-release combination of Diclegis®/Diclectin®, and do not possess the same fetal safety and efficacy data. As a result, their use should not be encouraged by healthcare providers.

Diclegis®/Diclectin® is the only safe and effective treatment for a pregnancy-related condition suffered by many millions of women. Wider re-introduction of Diclegis®/Diclectin® in other countries is necessary to give pregnant women worldwide the same safe and effective option for NVP—for which they have been orphaned from—that is available in Canada and the USA.

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References

1. Lacroix R, Eason E, Melzack R. Nausea and vomiting during pregnancy: a prospective study of its frequency, intensity, and patterns of change. Am J Obstet Gynecol. 2000;182(4):931–7.
2. Clark SM, Costantine MM, Hankins GD. Review of NVP and HG and early pharmacotherapeutic intervention. Obstet Gynecol Int. 2012;252676(10):24.
3. APGO. Nausea and vomiting of pregnancy. APGO Educational series on women's health issues. Boston: Jespersen & Associates, LLC; 2013.
4. Goodwin TM. Hyperemesis gravidarum. Obstet Gynecol Clin North Am. 2008;35(3):401–17.
5. Czeizel AE, Dudas I, Fritz G, Tecsoi A, Hanck A, Kunovits G. The effect of periconceptional multivitamin-mineral supplementation on vertigo, nausea and vomiting in the first trimester of pregnancy. Arch Gynecol Obstet. 1992;251(4):181–5.
6. Koren G, Maltepe C. Pre-emptive therapy for severe nausea and vomiting of pregnancy and hyperemesis gravidarum. J Obstet Gynaecol. 2004;24(5):530–3.
7. Bottomley C, Bourne T. Management strategies for hyperemesis. Best Pract Res Clin Obstet Gynaecol. 2009;23(4):549–64.
8. Verberg MF, Gillott DJ, Al-Fardan N, Grudzinskas JG. Hyperemesis gravidarum, a literature review. Hum Reprod Update. 2005;11(5):527–39.
9. Jueckstock JK, Kaestner R, Mylonas I. Managing hyperemesis gravidarum: a multimodal challenge. BMC Med. 2010;8(46):1741–7015.

10. Koch KL. Gastrointestinal factors in nausea and vomiting of pregnancy. Am J Obstet Gynecol. 2002;186(5 Suppl Understanding):S198–203.
11. Koch KL, Frissora CL. Nausea and vomiting during pregnancy. Gastroenterol Clin North Am. 2003;32(1):201–34.
12. Nguyen P, Einarson A. Managing nausea and vomiting of pregnancy with pharmacological and nonpharmacological treatments. Women's health (London, England). 2006;2(5):753–60. doi:10.2217/17455057.2.5.753.
13. Gill SK, Maltepe C, Koren G. The effect of heartburn and acid reflux on the severity of nausea and vomiting of pregnancy. Can J Gastroenterol. 2009;23(4):270–2.
14. Golberg D, Szilagyi A, Graves L. Hyperemesis gravidarum and Helicobacter pylori infection: a systematic review. Obstet Gynecol. 2007;110(3):695–703.
15. Sandven I, Abdelnoor M, Nesheim BI, Melby KK. Helicobacter pylori infection and hyperemesis gravidarum: a systematic review and meta-analysis of case–control studies. Acta Obstet Gynecol Scand. 2009;88(11):1190–200.
16. Vikanes AV, Stoer NC, Gunnes N, Grjibovski AM, Samuelsen SO, Magnus P, et al. *Helicobacter pylori* infection and severe hyperemesis gravidarum among immigrant women in Norway: a case–control study. Eur J Obstet Gynecol Reprod Biol. 2013;167(1):41–6.
17. Sherman PW, Flaxman SM. Nausea and vomiting of pregnancy in an evolutionary perspective. Am J Obstet Gynecol. 2002;186(5 Suppl Understanding):S190–7.
18. Fejzo MS, Macgibbon KW, Romero R, Goodwin TM, Mullin PM. Recurrence risk of hyperemesis gravidarum. J Midwifery Womens Health. 2011;56(2):132–6. doi:10.1111/j.1542-2011.2010.00019.x.
19. Fejzo MS, Ingles SA, Wilson M, Wang W, MacGibbon K, Romero R, et al. High prevalence of severe nausea and vomiting of pregnancy and hyperemesis gravidarum among relatives of affected individuals. Eur J Obstet Gynecol Reprod Biol. 2008;141(1):13–7.
20. Attard CL, Kohli MA, Coleman S, Bradley C, Hux M, Atanackovic G, et al. The burden of illness of severe nausea and vomiting of pregnancy in the United States. Am J Obstet Gynecol. 2002;186(5 Suppl Understanding):S220–7.
21. Lacasse A, Rey E, Ferreira E, Morin C, Berard A. Nausea and vomiting of pregnancy: what about quality of life? Bjog. 2008;115(12):1484–93.
22. Miller F. Nausea and vomiting in pregnancy: the problem of perception—is it really a disease? Am J Obstet Gynecol. 2002;186(5 Suppl Understanding):S182–3.
23. Mazzotta P, Stewart DE, Koren G, Magee LA. Factors associated with elective termination of pregnancy among Canadian and American women with nausea and vomiting of pregnancy. J Psychosom Obstet Gynaecol. 2001;22(1):7–12.
24. Piwko C, Ungar WJ, Einarson TR, Wolpin J, Koren G. The weekly cost of nausea and vomiting of pregnancy for women calling the Toronto Motherisk Program. Curr Med Res Opin. 2007;23(4):833–40.
25. Piwko C, Koren G, Babashov V, Vicente C, Einarson TR. Economic burden of nausea and vomiting of pregnancy in the USA. J Popul Ther Clin Pharmacol. 2013;20(2):10.
26. Weigel RM, Weigel MM. Nausea and vomiting of early pregnancy and pregnancy outcome. A meta-analytical review. Br J Obstet Gynaecol. 1989;96(11):1312–8.
27. Nulman I, Rovet J, Barrera M, Knittel-Keren D, Feldman BM, Koren G. Long-term neurodevelopment of children exposed to maternal nausea and vomiting of pregnancy and Diclectin. J Pediatr. 2009;155(1):45–50.
28. Veenendaal MV, van Abeelen AF, Painter RC, van der Post JA, Roseboom TJ. Consequences of hyperemesis gravidarum for offspring: a systematic review and meta-analysis. BJOG. 2011;118(11):1302–13.
29. van Oppenraaij RH, Jauniaux E, Christiansen OB, Horcajadas JA, Farquharson RG, Exalto N. Predicting adverse obstetric outcome after early pregnancy events and complications: a review. Hum Reprod Update. 2009;15(4):409–21.
30. Roseboom TJ, Ravelli AC, van der Post JA, Painter RC. Maternal characteristics largely explain poor pregnancy outcome after hyperemesis gravidarum. Eur J Obstet Gynecol Reprod Biol. 2011;156(1):56–9.
31. Einarson A, Maltepe C, Boskovic R, Koren G. Treatment of nausea and vomiting in pregnancy: an updated algorithm. Can Fam Physician. 2007;53(12):2109–11.
32. Jewell D, Young G. Interventions for nausea and vomiting in early pregnancy. Cochrane Database Syst Rev. 2003;4:CD000145.
33. Scorza K, Williams A, Phillips JD, Shaw J. Evaluation of nausea and vomiting. Am Fam Physician. 2007;76(1):76–84.
34. Gill SK, Einarson A. The safety of drugs for the treatment of nausea and vomiting of pregnancy. Expert Opin Drug Saf. 2007;6(6):685–94.
35. Brent RL. Bendectin: review of the medical literature of a comprehensively studied human nonteratogen and the most prevalent tortogen–litigen. Reprod Toxicol. 1995;9(4):337–49.
36. Einarson TR, Leeder JS, Koren G. A method for meta-analysis of epidemiological studies. Drug Intell Clin Pharm. 1988;22(10):813–24.
37. McKeigue PM, Lamm SH, Linn S, Kutcher JS. Bendectin and birth defects: I. A meta-analysis of the epidemiologic studies. Teratology. 1994;50(1):27–37.
38. Magee LA, Mazzotta P, Koren G. Evidence-based view of safety and effectiveness of pharmacologic therapy for nausea and vomiting of pregnancy (NVP). Am J Obstet Gynecol. 2002;186(5 Suppl Understanding):S256–61.
39. Koren G, Clark S, Hankins GD, Caritis SN, Miodovnik M, Umans JG, et al. Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trial. Am J Obstet Gynecol. 2010;203(6):16.
40. ACOG. ACOG (American College of Obstetrics and Gynecology) practice bulletin: nausea and vomiting of pregnancy. Obstet Gynecol. 2004;103(4):803–14.
41. SOGC. Clinical practice guidelines. The management of nausea and vomiting of pregnancy. J Obstet Gynaecol Can. 2002;24(10):817–23.
42. MothertoBaby. Nausea and vomiting. In: Maternal medical conditions fact sheets. http://www.mothertobaby.org/files/Nausea_and_Vomiting_7_13_2.pdf. 2013.
43. http://www.bendectin.com. Accessed: October 01, 2013.
44. Brent R. Bendectin and birth defects: hopefully, the final chapter. Birth Defects Res A Clin Mol Teratol. 2003;67(2):79–87.
45. Kutcher JS, Engle A, Firth J, Lamm SH. Bendectin and birth defects. II: ecological analyses. Birth Defects Res A Clin Mol Teratol. 2003;67(2):88–97.
46. Bendectin Peer Review Report 1975. Overall summary of 8-way Bendectin Study (unpublished study from the FDA databan DESI-10598). FDA1975 Contract No.: DESI 10598.
47. Ornstein M, Einarson A, Koren G. Bendectin/Diclectin for morning sickness: a Canadian follow-up of an American tragedy. Reprod Toxicol. 1995;9(1):1–6.
48. http://www.fda.gov/OHRMS/DOCKETS/98fr/080999e.pdf.Fr. Accessed: October 01, 2013.
49. Neutel CI, Johansen HL. Measuring drug effectiveness by default: the case of Bendectin. Can J Public Health. 1995;86(1):66–70.
50. Martindale: The complete drug reference. 37th ed. Database on the internet. London: Pharmaceutical Press; 2011.

51. Ottawa TCPA. Compendium of pharmaceuticals and specialties. Ottawa, ON. 2013. http://www.pharmacists.ca/index.cfm/education-practice-resources/canadian-drug-therapeutic-information/errata/errata-cps/#cps2013.
52. Vutyavanich T, Wongtra-ngan S, Ruangsri R. Pyridoxine for nausea and vomiting of pregnancy: a randomized, double-blind, placebo-controlled trial. Am J Obstet Gynecol. 1995;173(3 Pt 1):881–4.
53. Sahakian V, Rouse D, Sipes S, Rose N, Niebyl J. Vitamin B6 is effective therapy for nausea and vomiting of pregnancy: a randomized, double-blind placebo-controlled study. Obstet Gynecol. 1991;78(1):33–6.
54. Serafin WE, Babe KS. H1-receptor antagonists. In: Gilman AG, Hardman JG, Limbird LE, et al., editors. The pharmacological basis of therapeutics. New York: McGraw-Hill Companies; 1996. p. 586–692.
55. Koren G. Treating morning sickness PRN? Can Fam Physician. 2013;59(2):150–1.
56. Tani AS. Antihistamines. In: Olson K, editor. Poisoning & drug overdose. Norwalk: Appletin&Lange; 1998. p. 78–9.
57. Ganes DA, Midha KK. Identification in in vivo acetylation pathway for N-dealkylated metabolites of doxylamine in humans. Xenobiotica. 1987;17(8):993–9.
58. Gregory JF 3rd. Bioavailability of vitamin B-6. Eur J Clin Nutr. 1997;51(1):S43–8.
59. Mukherjee T, Hanes J, Tews I, Ealick SE, Begley TP. Pyridoxal phosphate: biosynthesis and catabolism. Biochim Biophys Acta. 2011;11(96):8.
60. di Salvo ML, Safo MK, Contestabile R. Biomedical aspects of pyridoxal 5'-phosphate availability. Front Biosci. 2012;4:897–913.
61. Duchesnay Inc. Diclectin product monograph. Blainville, Quebec, Canada. 2013. p. 1–24.
62. Nulman I, Koren G. Pharmacokinetic comparison of a delayed-release combination of doxylamine succinate and pyridoxine hydrocholoride (Diclectin) and oral solutions of these drugs in healthy women of childbearing age. Can J Clin Pharmacol. 2009;16(3):29.
63. Gill SK, Garcia-Bournissen F, Koren G. Systemic bioavailability and pharmacokinetics of the doxylamine-pyridoxine delayed-release combination (Diclectin). Ther Drug Monit. 2011;33(1):115–9.
64. Koren G, Vranderick M, Gill SK, Macleod S. Sex differences in the pharmacokinetics and bioequivalence of the delayed-release combination of doxylamine succinate–pyridoxine hydrochloride; implications for pharmacotherapy in pregnancy. J Clin Pharmacol. 2013;30(10):184.
65. Matok I, Clark S, Caritis S, Miodovnik M, Umans J, Hankins G, et al. Comparing the pharmacokinetics of doxylamine/pyridoxine delayed-release combination in nonpregnant women of reproductive age and women in the first trimester of pregnancy. J Clin Pharmacol. 2013;53(3):334–8.
66. Rowland JM, Slikker W Jr, Holder CL, Denton R, Prahalada S, Young JF, et al. Pharmacokinetics of doxylamine given as Bendectin in the pregnant monkey and baboon. Reprod Toxicol. 1989;3(3):197–202.
67. Geiger CJ, Fahrenbach DM, Healey FJ. Bendectin in the treatment of nausea and vomiting in pregnancy. Obstet Gynecol. 1959;14:688–90.
68. McGuinness BW, Binns DT. 'Debendox' in pregnancy sickness. J R Coll Gen Pract. 1971;21(109):500–3.
69. Wheatley D. Treatment of pregnancy sickness. Br J Obstet Gynaecol. 1977;84(6):444–7.
70. Bishai R, Mazzotta P, Atanackovic G, Levichek Z, Pole M, Magee LA, et al. Critical appraisal of drug therapy for nausea and vomiting of pregnancy: II. Efficacy and safety of Diclectin (doxylamine-B6). Can J Clin Pharmacol. 2000;7(3):138–43.
71. Ebrahimi N, Maltepe C, Bournissen FG, Koren G. Nausea and vomiting of pregnancy: using the 24-hour Pregnancy-Unique Quantification of Emesis (PUQE-24) scale. J Obstet Gynaecol Can. 2009;31(9):803–7.
72. Neutel I, Johansen HI. Variation in rates hospitalization for excessive vomiting in pregnancy by Bendectin/Diclectin use in Canada. Nausea and vomiting of pregnancy. State of the art. Toronto: The Motherisk Program; 2000. p. 54–9.
73. Gadsby R, Barnie-Adshead AM, Jagger C. A prospective study of nausea and vomiting during pregnancy. Br J Gen Pract. 1993;43(371):245–8.
74. Boskovic R, Einarson A, Maltepe C, Wolpin J, Koren G. Diclectin therapy for nausea and vomiting of pregnancy: effects of optimal dosing. J Obstet Gynaecol Can. 2003;25(10):830–3.
75. Atanackovic G, Navioz Y, Moretti ME, Koren G. The safety of higher than standard dose of doxylamine–pyridoxine (Diclectin) for nausea and vomiting of pregnancy. J Clin Pharmacol. 2001;41(8):842–5.
76. Costantine MM, Matok I, Chiossi G, Clark S, Miodovnik M, Umans JG, et al. Determinants of adherence to delayed-release doxylamine and pyridoxine in patients with nausea and vomiting of pregnancy. Ther Drug Monit. 2012;34(5):569–73.
77. Maltepe C, Koren G. Preemptive treatment of nausea and vomiting of pregnancy: results of a randomized controlled trial. Obstet Gynecol Int. 2013;2013:809787. doi:10.1155/2013/809787.
78. Brent R. Medical, social, and legal implications of treating nausea and vomiting of pregnancy. Am J Obstet Gynecol. 2002;186(5 Suppl Understanding):S262–6.
79. Koren G. The return to the USA of doxylamine-pyridoxine delayed release combination (Diclegis(R)) for morning sickness–a new morning for American women. J Popul Ther Clin Pharmacol. 2013;20(2):14.
80. Gibson JP, Staples RE, Larson EJ, Kuhn WL, Holtkamp DE, Newberne JW. Teratology and reproduction studies with an antinauseant. Toxicol Appl Pharmacol. 1968;13(3):439–47.
81. Hendrickx AG, Cukierski M, Prahalada S, Janos G, Rowland J. Evaluation of Bendectin embryotoxicity in nonhuman primates: I. Ventricular septal defects in prenatal macaques and baboon. Teratology. 1985;32(2):179–89.
82. Briggs GG, Roger K. Freemen, Yaffe SJ. Drugs in pregnancy and lactation. 9th ed. Philadelphia: Lippincott Williams&Wilkins; 2011.
83. Reprotox® database [electronic version] [homepage on the Internet] [database on the Internet]. 2013. Accessed: October 03, 2013.