

This manuscript accumulates and presents data and analysis already in the public domain; and as per the Journal's guidelines and expectations (see:<https://jhss.scholasticahq.com/about>) is not acceptable for publication as written.

What will make it much more interesting to the reader and publishable is if the authors incorporate and try to connect the physiological/ anatomical nerve connections to the nausea/vomiting reflex; then find evidence based literature that proves that connection by assigning acupoints to nerves associated through multiple mechanisms of nausea and vomiting.

For example, the ST36 and other acupointss are known to stimulate the vagus nerve, or modulate mechanisms (hormonal, neurotransmitter driven, muscular) of nausea and vomiting:

see, <https://doi.org/10.3748%2Fwjg.v25.i19.2315>, <https://doi.org/10.1155/2020/9357120>, <https://doi.org/10.1016/j.neuroimage.2004.02.017>,

<https://doi.org/10.1002/jmri.22006>,

<https://doi.org/10.1016/j.neuroimage.2004.02.017>

<https://doi.org/10.1177%2F1744806918783457>

<https://doi.org/10.1007/s40519-020-00864-0>

These are only a few references as examples, there are undoubtedly many more. These can then be used to speculate and or hypothesize on why certain clinical trials did not show significance (rather than just commenting that the sample size may have been too small).

Two tables will need to be presented in the manuscript to provide information. One, containing neural pathways/muscular/homonal/neurotransmitter pathways/chemoreceptor trigger zone, with their associated acupoints (and references)

second, the clinical studies that author dscusses, along with the acupoints and why they may or may not have been effective based on table 1.

Some references not mentioned appear below:

<https://doi.org/10.1016/j.heliyon.2024.e3096>

<https://doi.org/10.3390/healthcare12020218>

In summary, this manuscript has the potential to be much more than just a report on published literature. I look forward to reviewing the revised version incorporating my comments and references.

The following document highlights (in yellow) all newly added text where the author has added a secondary objective to address all the reviewer's comments. The author:

1. Connected the physiological/anatomical nerve connections to the nausea and vomiting reflexes, as shown in Table 1 and stated throughout the text,
2. Utilized the references suggested by the reviewer as well as additional sources to speculate and hypothesize as to why some clinical trials did not find statistical significance, and
3. Added tables 1 and 2, with table 1 containing the acupoints and their associated physiological pathways and table 2 containing the clinical studies the author discussed, along with the acupoints and why they may or may not have been effective based on mechanisms described in table 1.

Are Acupuncture and Acupressure Effective at the Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting in Children?

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Abstract

Acupuncture and acupressure are some of the most common non-pharmacological treatment modalities in the world, with evidence suggesting they may be useful in treating chronic diseases. There is a growing body of literature that suggests acupressure has positive effects towards treating chemotherapy-induced nausea and vomiting (CINV) in adults, but few trials and reviews have been conducted on the impact of acupressure in children. Thus, the primary objective of this review is to provide a robust and comprehensive summary of the existing literature on the efficacy of acupuncture and acupressure to treat CINV, with a specific focus on youth aged five to eighteen years. The secondary objective is to evaluate how the acupoints' anatomical and physiological nerve connections impact nausea and vomiting reflexes.

Although acupressure is becoming increasingly popular, there are still some accessibility barriers. Financially, four of the five countries in this review (USA, Germany, Taiwan, Brazil) include acupuncture in the public medical insurance. However, financially able citizens are more likely to use acupuncture compared to marginalized and vulnerable populations, living at or below the poverty threshold. The most effective acupoints were Pericardium 6 (PC-6), Large Intestines 4 (LI-4), and Stomach 36 (ST-36), which were referenced in five of the eight studies. However, wristbands targeting the PC-6 acupoint were ineffective at preventing CINV. Overall, acupressure was found to have beneficial effects in controlling CINV. The physiological mechanism of how acupuncture/acupressure reduces CINV was also explored. The findings suggested that acupuncture at ST-36 and PC-6 may stimulate the vagus nerve, vestibular system, and/or modulate neurotransmitters to help control nausea and vomiting. However, the physiological pathway of many other acupoints (including LI-4) were not researched or not publicly available. Future research should expand study sizes to detect statistically significant differences if they exist and focus on specific acupoints to determine the efficacy of each point, instead of using a variety of acupoints. Further investigation related to the physiological process in which acupuncture/acupressure reduces CINV should also be explored.

Keywords

Acupuncture, acupressure, acupressure, chemotherapy-induced nausea and vomiting, acupoint, vagus nerve, vestibular system

Introduction

Acupuncture is a widely known non-pharmacological treatment modality that involves the insertion of thin (usually solid filiform) needles into strategic points (acupoints) in the body to achieve specific therapeutic effects. The needles are usually manually manipulated depending on the practitioner, to further stimulate the acupoint (1). Acupuncture has existed for thousands of years and is rooted in traditional Chinese medicine (TCM) concepts and theories (2). It is becoming increasingly common in other countries around the world; out of reports from 129 countries, 80% recognize the use of acupuncture (3).

Acupressure is a similar traditional Chinese therapy that incorporates the same acupoints but through a non-invasive procedure (4). Practitioners use their hands, elbows, feet, or special devices to apply pressure to acupoints (5). While not as common as acupuncture, acupressure has become an increasingly popular alternative for those seeking a less invasive treatment.

Additionally, there is research that suggests acupuncture and acupressure (acotherapy/acotherapies) would be an appropriate and efficient treatment modality for chronic diseases (4). Thus, this would be especially beneficial in countries who are burdened by high rates of noncommunicable diseases. For example, cancer is the second leading cause of death globally; however, developed countries experience lower death rates than low- and middle-income countries (LMICs) despite having higher incidence rates of cancer. This may be due to the accessibility of treatment options to the citizens in high-income countries (6). Therefore, there is a greater use of cancer treatment in these developed countries that comes with numerous adverse side effects and additional risks.

Acupuncture is known to have beneficial effects on various musculoskeletal injuries such as chronic ankle instability as well as neurological conditions such as migraines (7-8). There have also been increasing numbers of studies investigating the efficacy of acupuncture in the prevention and treatment of chemotherapy-induced nausea and vomiting (CINV), a distressing side effect of chemotherapy that, if unaddressed, occurs in more than 90% of patients undergoing highly emetogenic chemotherapy (9). Some of the most prominent factors determining the severity of CINV are the chemotherapy regimen, dosage, and patient characteristics. Side effects can include malnutrition, loss of appetite, and electrolyte and hydration disorders in patients (10). In addition, the effects of CINV can decrease patient compliance, leading to unfinished treatments. Experiences of CINV can decrease a patient's quality of life by impacting their social and physical health.

The development of antiemetic drugs has mitigated the effects of CINV, but it is not an ideal solution due to various factors. The most commonly used antiemetic drugs are 5-hydroxytryptamine₃ receptor antagonists, neurokinin 1 receptor antagonists, corticosteroids, and olanzapine, an antipsychotic drug (11). The drugs have risks such as headaches and fatigue that can further add to the distress of the patient as well as high costs that could prevent patients from receiving the care they need (12). Additionally, around one-third of patients still suffer from CINV under antiemetic drugs (13). Therefore, non-pharmacological methods are required to mitigate CINV, such as acupuncture and acupressure.

The efficacy of antiemetic drugs may differ between adult and children's populations. However, most literature focuses on adult populations despite over 40% of children reporting that CINV is the most distressing side effect of chemotherapy (14). This indicates poor control of CINV in the children population that needs to be further explored. Experiencing CINV impacts the patient's quality of life and interferes with their ability to receive quality healthcare (15). Antiemetic medication has side

effects such as mood disturbances that can have further adverse impacts on the patient's mental and physical health (16). In addition, understanding the anatomical and physiological mechanisms of how acupoints stimulate the nerve connections to reduce the nausea and vomiting reflexes is necessary to ensure patients receive effective treatment. For example, the literature suggests that the pericardium 6 (PC-6) and stomach 36 (ST-36) acupoints stimulate the vagus nerve directly, promoting parasympathetic activity and increasing gastric motility (17). Understanding exactly how the acupoints affect nausea and vomiting reflexes can lead to improved treatment options for children experiencing CINV.

There have been few trials and reviews conducted on acupoints and CINV in children's populations. Childhood cancers should be examined separately from cancer in adults because they have different clinical behaviors, origins, and treatment modalities (18). In addition, cancer is the leading cause of death in pediatric and young adult populations in the US (19) and it is more fatal in low- and middle-income countries (20). While there have been some studies on the impact that acupuncture and acupressure have on children experiencing CINV, these have not yet been summarized into a comprehensive review. Thus, the primary objective of this review is to provide a robust and comprehensive summary of the existing literature on the efficacy of acupuncture and acupressure to treat CINV, with a specific focus on youth aged five to eighteen years. The secondary objective is to evaluate how the acupoints' anatomical and physiological nerve connections impact nausea and vomiting reflexes.

CINV in children in high-income countries

Seventy-five percent (six out of eight) of the articles included in this review were published in high-income countries. Of these articles, three were published based on data from the United States, two from Germany, and one from Taiwan.

Accessibility of acupuncture/acupressure and how it's portrayed as an option for children with CINV

In the United States, acupuncture and acupressure are often available as an additional treatment option rather than standard of care. Although only 1.5% of the US population has used acupuncture, there has been a 257% increase in total licensed acupuncturists from 1988, demonstrating a dramatic increase in licensed and practicing acupuncturists (21-22). According to the US Bureau of Labor Statistics, there were approximately 7,800 acupuncturists employed as of May 2022 (23). The states with the highest number of acupuncturists include California, Florida, New York, and Washington (22). Although Washington has a high number of acupuncturists, acupuncture is not often offered as a standalone treatment option. For example, at the Seattle Children's Hospital, acupuncture is often a complementary treatment in addition to a primary treatment option (24). In fact, there were only one part-time acupuncturist, and three physicians trained in acupuncture at the time the study was conducted (24). One study used a generalized estimating equations analysis to find that children were more likely to use acupuncture than adults and adolescents with a Hispanic mother were more likely to use acupuncture than non-Hispanic adolescents (25). The results also suggested that people in the working-class were less inclined to use acupuncture (25). There is not a breadth of statistics available on acupressure in terms of its prevalence which may be because of varying license requirements to practice in the US (26). However, it can be inferred that while acupoints have become increasingly popular, they still are not an option that many are presented with when they encounter health-related issues.

Financial restraints may also contribute to accessibility issues in the United States. Various private insurance plans such as Health Net, United Healthcare, and Aetna have covered acupuncture for

many years (27). Some government-run programs including Medicare and the Veterans Administration also added acupuncture to their benefits in 2020. However, many insurance companies do not employ acupuncturists, as three US states have not officially recognized acupuncture as a valid and effective treatment option, which makes it difficult or impossible to bill them for their services (27). Additionally, out-of-pocket expenses for such therapies may not be affordable to the public, thus furthering this inaccessibility.

Countries such as Germany and Taiwan utilize acutherapies more than the United States. It is estimated that a third of German medical doctors utilize this therapy in their own practices (28). Another study based in Germany stated that acupuncture is the most prominent and popular complementary medicine treatment in the healthcare system (29). However, there is an association between the use of acupuncture and older age; this suggests that it may not be presented as a common option for many children. Financially, acupuncture has been reimbursed by German health insurance since 2007 (30). Similarly, acupuncture services are under the National Health Insurance in Taiwan, and there was a higher prevalence of acupuncture usage (11%) in 2011 compared to utilization in the United States (31).

Common acupoints used

In the included articles, some of the most frequently used acupoints include the Stomach 36 (ST-36), Pericardium 6 (PC-6), and Large Intestines 4 (LI-4), which were referenced in 50% of the articles (16, 24, 32). All three of the articles that referenced these acupoints compared them with sham acupuncture and found that these acupoints were positively correlated with the occurrence of vomiting and the severity of nausea more so than the sham acupuncture, but two (Reindl et al., 2006 and Yeh et al., 2012) were unable to achieve a statistically significant outcome due to the limited number of participants. Another article found the use of antiemetic medication and occurrence of vomiting decreased significantly in the intervention group compared to the sham group (32). Other acupoints include five reflex points on the ear, in a form of auricular acupressure (14). However, these also led to unclear results due to the small study size and other rationale provided below. Finally, the last two studies used acupressure wristbands at the acupoint PC-6 but found that it was not more effective than placebo (33-34).

Responses to treatment and studies' limitations

In addition to evaluating the efficacy of acupressure and acupuncture, all six articles from high-income countries used a standard amount of antiemetic medication for all participants. Two of the articles demonstrated increased control of CINV from acupuncture and acupressure (24, 32). Another two of the articles found that acupressure was not more useful than the sham group (33-34). The last two articles noted that patients in the intervention group reported lower severity and occurrence of nausea and vomiting (14, 16). However, the findings were not statistically significant which is mostly due to the insufficient study size, thus not having enough statistical power to detect a statistical difference, if there was one. Based on the power calculation, 35 participants were needed in the trial by Reindl et al., but due to attrition, only five patients were followed through to the end of the study. In addition to both studies not having sufficient sample size to achieve the desired statistical power, some other possibilities include how both studies used self-reported questionnaires which are more prone to attrition, selection, and recall biases given the subjectiveness.

There may be multiple other reasons as to why acupuncture was not statistically effective in these two studies. For example, in the study by Yeh et al., the researchers had two groups (sham and intervention) in which they stimulated auricular acupoints in accordance with Dr. Huang's ear reflex theory for the intervention and sham groups (14). Auricular acupoints are rarely used to treat nausea

and vomiting in the clinical setting. The acupoints in the intervention group included shenmen, sympathetic, cardia, stomach, and digestive subcortex (Table 1), which were known to treat nausea and/or vomiting according to Dr. Huang's ear reflex theory (Table 2); whereas the sham group had acupoints that were not known to treat nausea and/or vomiting (14). Given the physiological pathways of the acupoint are unclear (Table 1), the statistically insignificant findings may have been due to the placebo effect in the sham acupressure group. For example, in the sham group, participants may have reported reduced nausea and vomiting because they believed they were receiving the intervention. This could have resulted in a small difference in the reduction of CINV between the sham and intervention groups, and given the insufficient sample size, there would not have been enough statistical power to detect such a small difference. Additional possibilities that may have resulted in statistical insignificance of the results are that the children's population may not be the most reliable as they may not be able to accurately recall the impact of the acupuncture. Whereas in the study by Reindl et al., since the acupuncturist was a human, results are subject to human errors. For example, placing the acupuncture needle in the wrong position or depth may cause the acupoint to not be stimulated properly, which would alter or affect the results (Table 2). Additionally, given the randomized study design, Reindl et al. did not conduct an Intent to Treat or a Mixed-Effect Model analysis to ensure findings were robust (16).

Table 1. Physiological pathways and their associated acupoints

Acupoints	Neural/muscular/hormonal/neurotransmitter pathways
ST-36	Studies have shown that electroacupuncture at ST-36 seems to mitigate nausea and vomiting through a complex vagovagal pathway in rats (17). Acupuncture stimulates the sensory nerves at the ST-36 acupoint which travel through afferent nerve fibers to stimulate the dorsal motor nucleus of the vagus nerve, which controls involuntary movements of the digestive tract (17). This may promote gastric motility, which in turn reduces nausea (17, 35). This is further supported by a vagotomy in the rats, which completely abolished the increase in gastric motility that was observed after electroacupuncture at ST-36 (17). While this study focused on rats as test subjects, there have been some studies that show that the vagus nerve is stimulated in acupuncture in humans as well (36-40), but not much detail on the mechanisms was provided. One can infer that the physiological pathway that stimulates the vagus nerve in rats is similar to that of humans. One study found that electroacupuncture at ST-36 stimulates the sciatic nerve, which causes signals to be transmitted to the vagus nerve, although the mechanism as to how this occurs is unknown (40). However, many articles that have made this claim are not peer-reviewed articles.
PC-6	Though the literature is sparse regarding the acupoint PC-6, scientists have reported that the acupoint PC-6 has been shown to selectively activate areas of the cerebellum (the nodulus and uvula) that are specifically involved in vestibular control and alleviates symptoms of motion sickness and nausea (41-42). It has also been suggested that acupuncture at PC-6 facilitates the release of neurotransmitters which may desensitize responses of the chemoreceptor trigger zone or vomiting center in the medulla, thus resulting in decreased nausea and vomiting (42).
LI-4*	The LI-4 acupoint is known to provide pain relief (43). However, based on non-

	peer reviewed literature, acupressure at the combination of both LI-4 and ST-36 seems to be effective for preventing nausea (44). Additionally, peer-reviewed literature suggests that acupuncture at both PC-6 and LI-4 acupoints alongside antiemetic drugs (in both the control and intervention group), reduced nausea intensity as well as postoperative nausea and vomiting (45). A similar study also found that acupuncture at PC-6 and LI-4 was more effective at reducing postoperative nausea and vomiting than acupuncture at PC-6 alone (46). Based on this information, one can hypothesize that the LI-4 acupoint is effective in combination with other acupoints (ST-36 and PC-6), but more research is needed on the effectiveness of LI-4 alone when treating nausea and vomiting.
CV-12*	CV-12 has often been used in conjunction with PC-6 and/or ST-36 when treating nausea. On its own, it has been known to rectify digestion-related issues, such as bloating, constipation, and vomiting.
Auricular acupoints [†]	This group of acupoints (shenmen, sympathetic, cardia, stomach, digestive subcortex) was cited in Dr. Huang's ear reflex theory (47). One physiological pathway to experiencing CINV is through the interaction of emetic drugs with dopamine receptors in the chemoreceptor trigger zone. This activates the nucleus tractus solitarius, which can initiate the emetic response. Thus, it is possible that the stimulation of auricular acupoints will decrease the sensitivity of the dopamine receptors, thus decreasing the severity of the CINV.
BL-20*	This acupoint has been traditionally used to treat digestion-related issues such as vomiting and emesis. It has been shown to decrease xylazine induced emesis in dogs.
SP-6*	The SP-6 acupoint is most commonly used to treat labor or menstrual related pains but it has also been shown to be effective in treating postoperative nausea and vomiting.
KD-3*	This acupoint is usually used to treat sleep, energy, and weight irregularities. However, many articles that have made this claim are not peer-reviewed.

Note

*: There is no clear evidence on specific physiological pathways for the following acupoints but listed below are the conditions these acupoints are typically known to treat.

†: There is no publicly available evidence on the specific physiological pathway for the following acupoints but listed are the conditions these acupoints are typically known to treat.

Table 2. Effectiveness of reducing CINV with acupuncture/acupressure versus conventional treatment

Study	Results	Acupoints	Why findings may or may not have been effective
Yeh et al., 2012	Findings were not statistically significant between the acupuncture group and	Auricular acupoints (shenmen, sympathetic,	There is no scientific evidence supporting Dr. Huang's ear reflex theory being effective in reducing nausea and vomiting. However, it

	sham acupuncture group, with a reduction in CINV in the intervention group.	cardia, stomach, digestive subcortex)	is possible that these acupoints were unsuccessful in modulating the sensitivity of the dopamine receptors (See pathological pathway for auricular acupuncture in Table 1).
Reindl et al., 2008	Findings were not statistically significant between the acupuncture and control group but found that acupuncture could be effective at reducing CINV.	Acupoints were chosen by the acupuncturist to tailor to the patients' needs, most commonly used acupoints were PC6, ST36, CV12, LI4	ST36 and PC6 may not have been stimulated enough to have modulated the vagus nerve, vestibular system, and/or neurotransmitter activity (See pathological pathway for PC6 and ST36 acupoints in Table 1). Since the administrator of the acupuncture was a person, it was subject to human error, one of which could be misplacing the acupuncture needle close to the acupoint, thus causing the effects of the acupoints to be compromised.
Ralston-Wilson, 2013	Findings were statistically significant and found that acupuncture decreased CINV.	ST36, LI4, KD3, SP6, PC6	ST36 and PC6 modulated the vagus nerve, vestibular system, and/or chemotherapy trigger zone which reduced nausea and vomiting. LI4 was also effectively stimulated as it was used alongside PC6 and/or ST36. (See pathological pathway for PC6, ST36, and LI4 acupoints in Table 1.)
Gottschling et al., 2008	Findings were statistically significant between the acupuncture group and no acupuncture group, with a significant reduction in the need for antiemetics in the acupuncture group.	PC6, ST36, CV12, LI4	ST36 and PC6 modulated the vagus nerve, vestibular system, and/or chemotherapy trigger zone which reduced nausea and vomiting. LI4 was also effectively stimulated as it was used alongside PC6 and/or ST36. (See pathological pathway for PC6, ST36, and LI4 acupoints in Table 1.)
Dupuis, 2018	Findings were not significant; acupressure wristbands did not reduce CIN in	PC6	PC6 wristbands may not have exerted enough pressure to stimulate the pathways that the PC6 acupoint usually stimulates.

	the acute or delayed phases.		(See pathological pathway for PC6 in Table 1.)
Jones et al., 2008	Findings were not significant; acupressure wristbands did not cause a significant reduction in nausea or vomiting.	PC6	PC6 wristbands may not have exerted enough pressure to stimulate the pathways that the PC6 acupoint usually stimulates. (See pathological pathway for PC6 in Table 1.)
Varejão et al., 2019	Findings were statistically significant, showing that laser acupuncture was effective at relieving nausea and vomiting	PC6, LI-4, ST-36, BL-20, and SP-6	ST36 and PC6 modulated the vagus nerve, vestibular system, and/or chemotherapy trigger zone which reduced nausea and vomiting. LI4 was also effectively stimulated as it was used alongside PC6 and/or ST36. (See pathological pathway for PC6, ST36, and LI4 acupoints in Table 1.)
Abusaad et al., 2015	Findings demonstrated that acupuncture significantly decreased nausea, vomiting, and retching.	PC6	PC6 modulated the vestibular system, and/or chemotherapy trigger zone which reduced nausea and vomiting. (See pathological pathway for the PC6 acupoint in Table 1.)

CINV in children in LMICs

Twenty-five percent (two out of eight) of the articles included in this review were published in LMICs. Of these articles, one was published in Egypt while the other was published in Brazil.

Accessibility of acupuncture/acupressure and how it's portrayed as an option for children with CINV

The practice of traditional Chinese medicine in Brazil, including acupuncture and acupressure, began with the arrival of Chinese immigrants in the early 1800s (48). Since then, many immigrants and native Brazilians have participated in this treatment. In fact, it is believed that there are approximately 160,000 acupuncturists in Brazil according to the Federation of Acupuncturists of Brazil (48). Despite the abundance of professional acupuncturists in Brazil, not all citizens utilize their services. Wealthy individuals, or those who had a higher education and a private health plan, are more likely to use integrative and complementary practices such as acupuncture and acupressure (49). There is limited data available on acupressure regarding the utilization, the number of certified individuals, and the number of facilities that offer acupressure services, as acupuncture is much more commonly practiced in Brazil. In terms of financial accessibility, acupuncture is included in the health insurance provided by the Sistema Único de Saúde, Brazil's national health service (50). However, it is rarely used compared to its usage with private health insurances (50).

In Egypt, there is only one acupuncture clinic in public hospitals as of 2016 (51). Although an increasing number of doctors have become more interested in acupuncture, there is no formal acupuncture educational training or legal regulations on its practice, which means there is no uniform way to learn or practice acupuncture (51). Additionally, it is not covered by medical insurance, furthering its inaccessibility to civilians (52). While there are numerous research articles published on acupressure and its effects in Egypt, there are no statistics regarding the prevalence of acupressure.

Common acupoints used

One hundred percent (two of two) of the articles from LMICs referenced the PC-6 acupoint in their intervention group, located on the inside of one's wrist (53-54). However, one article also referenced the LI-4, ST-36, BL-20, and SP-6 acupoints (53). By referencing only one acupoint, one can determine the efficacy of that acupoint in treating CINV. However, using multiple acupoints allowed acupuncturists to individualize the treatment plan according to the patient, which may lead to better results.

Responses to treatment

In addition to evaluating the efficacy of acupressure and laser acupuncture, all articles from LMICs used a standard level of antiemetic medication for all participants. The responses to the acuthery were positive in both studies. Researchers of the Brazil study found laser acupuncture to be effective at relieving nausea five days after chemotherapy as well as vomiting two and three days after chemotherapy (53). Researchers of the Egypt study found that acupressure on the PC-6 point significantly reduced nausea, retching, and vomiting in the participants (54).

A direct comparison of high vs. LMICs: acupuncture/acupressure for children with CINV

Accessibility

Acupuncture and acupressure are becoming increasingly popular around the world, but of the countries included in this review, the United States is most prominent. The accessibility of acupuncture in Taiwan suggests that Asian countries who are in close geographic proximity to China are more likely to use traditional Chinese medicine such as acupuncture and acupressure. Similarly, Brazil, which has had many Chinese immigrants since the 1800s, also has a higher prevalence of acupuncture (48). Additionally, Germany seems to have also deeply implemented this therapy into their healthcare system despite its more westernized culture. The only country that had significantly poor access to acupuncture is Egypt. However, the increasing number of studies published in Egypt suggests that acutheries may become more widespread in the future.

Financially, four of the five countries (USA, Germany, Taiwan, Brazil) include acupuncture in the public medical insurance. However, in the US and Brazil, acupuncture is more commonly used in private medical insurance plans. In both these countries, financially able citizens are more likely to use acupuncture compared to marginalized and vulnerable populations, those living at or below the poverty threshold, who utilize other complementary therapies. Given both private and public medical insurances cover acupuncture services, those with private insurance utilize these services more often (50). This could be due to them having more knowledge and understanding of the benefits of acupuncture. Whereas vulnerable populations with public insurance may not be as knowledgeable of the benefits of acupuncture or that it is even covered by their insurance. Overall, while acutheries seem to be more popular amongst the upper-class, it is becoming more widespread around the world.

Acupoints used

The most popular acupoint for treating CINV in children is the Pericardium-6 (PC-6) acupoint, which was referenced in five research articles (16, 24, 32, 53-54). However, there were various other

acupoints that were commonly referenced such as Large Intestine-4 (LI-4) and Stomach-36 (ST-36), which were included in four articles (16, 24, 32, 53). These acupoints are also often referenced in studies on the efficacy of acupuncture on CINV in adults and seem to have a positive impact in preventing and minimizing the effects of CINV (55-56). The PC-6, ST-36, and LI-4 acupoints are also commonly used to treat nausea and vomiting even without the presence of chemotherapy (57). Thus, it makes sense that these acupoints would be effective for treating CINV given that they are already used for treating nausea and vomiting.

Responses to treatment and studies' limitations

Of the eight studies included in this review, four studies found acuthery to be effective at preventing nausea and vomiting (24, 32, 53-54). Two studies saw positive impacts of acuthery on CINV outcomes but due to their small study sizes and perhaps an inability to properly stimulate the acupoints (Table 2), these findings were not statistically significant (14, 16). Furthermore, two studies found acuthery to not be more effective than the placebo in preventing CINV (33-34). These studies both used acupressure wrist bands with acupoint PC-6. The PC-6 acupoint is commonly used amongst the other studies and has been shown to have beneficial effects in the prevention and treatment of CINV (16, 24, 32, 53-54). Thus, it can be inferred that acupressure wrist bands may not have exerted enough pressure to stimulate the PC-6 acupoint (33-34).

Evaluation of the neural pathways involved in triggering nausea and vomiting

Steps of neural pathway of acupoint

Studies have shown that electroacupuncture at ST-36 seems to mitigate nausea and vomiting through a complex vagovagal pathway in rats (17). Based on experimental research, one can infer that the physiological pathway that stimulates the vagus nerve in rats is similar to that of humans. Another study found that electroacupuncture in humans at ST36 stimulated the sciatic nerve which can send signals to the vagus nerve (40) (Table 1).

Though the literature is sparse regarding the acupoint PC-6, scientists have reported that the acupoint PC-6 is involved in vestibular control and modulating the chemotherapy trigger zone, which may result in decreased nausea and vomiting (Table 1).

While the LI-4 acupoint is known to provide pain relief (43), there have not been many studies evaluating the efficacy or physiological mechanism of the LI-4 acupoint alone on treating nausea and vomiting (Table 1). However, there is evidence that the LI-4 acupoint, when combined with PC-6 or ST-36, can exacerbate their effects in reducing CINV (Table 1) (44-46).

Limitations

One of the most prominent limitations of this review is how little research has been conducted on the efficacy of acuthery for CINV in children. To minimize the impact of this, literature was searched across multiple databases, such as the National Center for Biotechnology Information (NCBI) and Google Scholar for articles that may be available on one database and not the other. Additional literature was found by reading cited articles that were relevant to this topic.

The literature is also limited as it relates to the general accessibility of acuthery in the research setting (only one article described the accessibility). To minimize the impact of this, other literature was explored to find statistics on the accessibility of acuthery in relevant countries that was not provided in the literature. However, while this was able to provide a general idea of the prevalence of acuthery, it may not accurately reflect the situation in the research setting.

Finally, there was not a lot of publicly available literature on certain acupoints (auricular acupoints) and their mechanisms as well as not enough peer-reviewed literature on how some acupoints are stimulated to reduce CINV. To mitigate this, non-peer reviewed articles were cited when the information was consistent across multiple sources. Additionally, hypotheses for the physiological pathway of the auricular acupoints were created based on the publicly available literature.

Future research

Future research should explore the accessibility of acupressure and acupuncture in the research setting more, as it provides insight into the prevalence and the standardization of this therapy. Additionally, randomized control trials with more participants should be conducted to provide enough statistical power to identify differences if they exist. Researchers should consider focusing on specific acupoints to determine the efficacy of each point, instead of using a variety of acupoints. Finally, the physiological pathways and mechanisms of how stimulating acupoints such as LI-4, CV-12, and the auricular acupoints would reduce nausea and vomiting should be explored, and researchers should be sure to properly stimulate each acupoint to achieve the desired effect.

Conclusion

Given the evidence provided in the trial studies, acupressure and acupuncture may be effective options for the prevention and treatment of CINV in children. More specifically, acupoints PC-6, ST-36, and LI-4 were effective in controlling CINV whereas auricular acupoints were not. However, acupressure wristbands that target the PC-6 acupoint were shown to be ineffective based on findings from two studies (33-34). While acupuncture is becoming increasingly popular around the world as an alternative medicine, there are still accessibility barriers such as insurance coverage that prevents people from using this therapy. Additionally, while there is literature on how acupuncture at PC-6 and ST-36 reduce CINV, there remains many acupoints such as LI-4, CV-12, and auricular acupoints that do not have an outline of their physiological pathways. Thus, future research should take into consideration the accessibility of acupressure and acupuncture to reveal its practical implications as well as focus on specific acupoints to determine their effectiveness. Researchers should also conduct more trials of the physiological pathways of specific acupoints. Research studies with more participants are needed to have adequate power to detect a statistically significant difference, if one exists, which will determine whether these therapies are truly effective in prevention and treatment of CINV in children.

Acknowledgements

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Abbreviations

CINV	Chemotherapy-induced nausea and vomiting
PC-6	Pericardium 6
LI-4	Large Intestines 4
ST-36	Stomach 36
TCM	Traditional Chinese medicine
LMIC	Low- and middle-income countries

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Thank you for addressing my comments. The paper is much improved. However, some references are still missing from the manuscript (see below).

1. Please include meta-analyses references in these references in the manuscript, for example Table 3 in <http://dx.doi.org/10.1016/j.autneu.2006.07.015>, include that timing of acupuncture as presented in <https://e-century.us/files/ijcem/13/10/ijcem0112962.pdf>, i.e. before or after chemotherapy, see the Limitations section (difficulty of sham and the placebo effect)

in <https://www.reliasmedia.com/articles/115843-acupuncture-as-an-antiemetic-is-there-a-point>

2. To further the conversation and discussion about how to distinguish and disentangle the placebo effect from acupuncture, I would like you to propose the following design for a clinical study (or your equivalent), in this table 'sham' stands for a sham acupuncture procedure, +1 is effect, 0 is no effect, pill stands for standard antiemetic tablet.

Sham+pill acupuncture+pill acupuncture only

+1` +1 0

0 +1 +1

+1 0 +1

The first row results mean that only pill is effective, the second row results mean that only acupuncture is effective and the third row results mean that only sham (placebo) is effective.

This proposal has not yet appeared in the literature and will address the long standing conundrum about the placebo effect in acupuncture procedures.

You are free to think of other ways to go about this. For example, you could probably conceive columns with headings sham+pill, sham + sugar pill, acupuncture+pill, acupuncture+ sugar pill, acupuncture only. You could then assign random values to each column between 0 and 1 to definitively assign the cause of the effect to the acupuncture procedure (or not).

With these two points properly addressed, I think your paper will add significant value to the existing corpus of knowledge in the field.

<http://dx.doi.org/10.1016/j.autneu.2006.07.015> (Table 3 on mechanisms is particularly informative for inclusion in the manuscript).

<https://doi.org/10.3390/vetsci8080149>

<https://doi.org/10.1200/JCO.2005.06.028>

<https://e-century.us/files/ijcem/13/10/ijcem0112962.pdf>

<https://www.reliasmedia.com/articles/115843-acupuncture-as-an-antiemetic-is-there-a-point>

The following document highlights (in yellow) all newly added text where the author has added a secondary objective to address all the reviewer's comments. The author:

4. Included meta-analyses references in this manuscript;
 5. Considered the timing of acupuncture and how that can impact study results;
 6. Included more information on the difficulty of sham acupuncture and the placebo effect;
 7. Proposed a randomized control trial to further the discussion of how to distinguish the placebo effect from acupuncture.
-

Are Acupuncture and Acupressure Effective at the Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting in Children?

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Abstract

Acupuncture and acupressure are some of the most common non-pharmacological treatment modalities in the world, with evidence suggesting they may be useful in treating chronic diseases. There is a growing body of literature that suggests acuthery has positive effects towards treating chemotherapy-induced nausea and vomiting (CINV) in adults, but few trials and reviews have been conducted on the impact of acuthery in children. Thus, the primary objective of this review is to provide a robust and comprehensive summary of the existing literature on the efficacy of acupuncture and acupressure to treat CINV, with a specific focus on youth aged five to eighteen years. The secondary objective is to evaluate how the acupoints' anatomical and physiological nerve connections impact nausea and vomiting reflexes.

Although acuthery is becoming increasingly popular, there are still some accessibility barriers. Financially, four of the five countries in this review (USA, Germany, Taiwan, Brazil) include acupuncture in the public medical insurance. However, financially able citizens are more likely to use acupuncture compared to marginalized and vulnerable populations, living at or below the poverty threshold. The most effective acupoints were Pericardium 6 (PC-6), Large Intestines 4 (LI-4), and Stomach 36 (ST-36), which were referenced in five studies. However, wristbands targeting the PC-6 acupoint were ineffective at preventing CINV. Overall, acuthery was found to have beneficial effects in controlling CINV. The physiological mechanism of how acupuncture/acupressure reduces CINV was also explored. The findings suggested that acupuncture at ST-36 and PC-6 may stimulate the vagus nerve, vestibular system, and/or modulate neurotransmitters to help control nausea and vomiting. However, the physiological pathway of many other acupoints (including LI-4) were not researched or not publicly available. Future research should expand study sizes to detect statistically significant differences if they exist and focus on specific acupoints to determine the efficacy of each point, instead of using a variety of acupoints. Further investigation related to the physiological process in which acupuncture/acupressure reduces CINV should also be explored.

Keywords

Acupuncture, acupressure, acuthery, chemotherapy-induced nausea and vomiting, acupoint, vagus nerve, vestibular system

Introduction

Acupuncture is a widely known non-pharmacological treatment modality that involves the insertion of thin (usually solid filiform) needles into strategic points (acupoints) in the body to achieve specific therapeutic effects. The needles are usually manually manipulated depending on the practitioner, to further stimulate the acupoint (1). Acupuncture has existed for thousands of years and is rooted in traditional Chinese medicine (TCM) concepts and theories (2). However, it is becoming increasingly common in other countries around the world; out of reports from 129 countries, 80% recognize the use of acupuncture (3).

Acupressure is a similar traditional Chinese therapy that incorporates the same acupoints but through a non-invasive procedure (4). Practitioners use their hands, elbows, feet, or special devices to apply pressure to acupoints (5). While not as common as acupuncture, acupressure has become an increasingly popular alternative for those seeking a less invasive treatment.

Additionally, there is research that suggests acupuncture and acupressure (acupuncture therapy) would be an appropriate and efficient treatment modality for chronic diseases (4). Thus, this would be especially beneficial in countries who are burdened by high rates of noncommunicable diseases. For example, cancer is the second leading cause of death globally; however, developed countries experience lower death rates than low- and middle-income countries (LMICs) despite having higher incidence rates of cancer. This may be due to the accessibility of treatment options to the citizens in high-income countries (6). Therefore, there is a greater use of cancer treatment in these developed countries that comes with numerous adverse side effects and additional risks.

Acupuncture is known to have beneficial effects on various musculoskeletal injuries such as chronic ankle instability as well as neurological conditions such as migraines (7-8). There have also been increasing numbers of studies investigating the efficacy of acupuncture in the prevention and treatment of chemotherapy-induced nausea and vomiting (CINV), a distressing side effect of chemotherapy that, if unaddressed, occurs in more than 90% of patients undergoing highly emetogenic chemotherapy (9). Some of the most prominent factors determining the severity of CINV are the chemotherapy regimen, dosage, and patient characteristics. Side effects can include malnutrition, loss of appetite, and electrolyte and hydration disorders in patients (10). In addition, the effects of CINV can decrease patient compliance, leading to unfinished treatments. Experiences of CINV can decrease a patient's quality of life by impacting their social and physical health.

The development of antiemetic drugs has mitigated the effects of CINV, but it is still not an ideal solution. The most commonly used antiemetic drugs are 5-hydroxytryptamine₃ receptor antagonists, neurokinin 1 receptor antagonists, corticosteroids, and olanzapine, an antipsychotic drug (11). The drugs have risks such as headaches and fatigue that can further add to the distress of the patient as well as high costs that could prevent patients from receiving the care they need (12). Additionally, around one-third of patients still suffer from CINV under antiemetic drugs (13). Therefore, non-pharmacological methods are required to mitigate CINV, such as acupuncture and acupressure.

The efficacy of antiemetic drugs may differ between adult and children populations. However, most literature focuses on adult populations despite over 40% of children reporting that CINV is the most distressing side effect of chemotherapy (14). This indicates poor control of CINV in the children population that needs to be further explored. Experiencing CINV impacts the patient's quality of life and interferes with their ability to receive quality healthcare (15). Antiemetic medication has side effects such as mood disturbances that can have further adverse impacts on the patient's mental and

physical health (16). In addition, understanding the anatomical and physiological mechanisms of how acupressure pinpoints specific acupoints that stimulate the nerve connections to reduce the nausea and vomiting reflexes is necessary to ensure patients receive effective treatment. For example, the literature suggests that pericardium 6 (PC-6) and stomach 36 (ST-36) stimulate the vagus nerve directly, promoting parasympathetic activity and increasing gastric motility (17). Understanding exactly how the acupoints affect nausea and vomiting reflexes can lead to improved treatment options for children experiencing CINV.

There have been few trials and reviews conducted on acuthery and CINV in children populations. Childhood cancers, although relatively rare, should be examined separately from cancer in adults because they have different clinical behaviors, origins, and treatment modalities (18). In addition, cancer is still the leading cause of death in pediatric and young adult populations in the US (19) and it is more fatal in low- and middle-income countries (20). However, while there have been some studies on the impact that acupuncture and acupressure have on children experiencing CINV, these have not yet been summarized into a comprehensive review. Thus, the primary objective of this review is to provide a robust and comprehensive summary of the existing literature on the efficacy of acupuncture and acupressure to treat CINV, with a specific focus on youth aged five to eighteen years. The secondary objective is to evaluate how the acupoints' anatomical and physiological nerve connections impact nausea and vomiting reflexes.

CINV in children in high-income countries

Seventy-five percent (six out of eight) of the articles included in this review were published in high-income countries. Of these articles, three were published in the United States, two were published in Germany, and one was published in Taiwan.

Accessibility of acupuncture/acupressure and how it's portrayed as an option for children with CINV

In the United States, acupuncture and acupressure are often available as an additional treatment option and not as a standard of care. Although only 1.5% of the US population has used acupuncture, there has been a 257% increase in total licensed acupuncturists from 1988, demonstrating a dramatic increase in licensed and practicing acupuncturists (21-22). According to the US Bureau of Labor Statistics, there were approximately 7,800 acupuncturists employed as of May 2022 (23). The states with the highest number of acupuncturists include California, Florida, New York, and Washington (22). Although Washington has a high number of acupuncturists, acupuncture is not often offered as a standalone treatment option. For example, at the Seattle Children's Hospital, acupuncture is often a complementary treatment in addition to a primary treatment option (24). In fact, there were only one part-time acupuncturist and three physicians trained in acupuncture at the time the study was conducted (24). One study used a generalized estimating equations analysis to find that children were more likely to use acupuncture than adults and adolescents with a Hispanic mother were more likely to use acupuncture than non-Hispanic adolescents (25). The results also suggested that people in the working-class were less inclined to use acupuncture (25). There is not a breadth of statistics available on acupressure in terms of its prevalence which may be because of varying license requirements to practice in the US (26). However, it can be inferred that while acutherapies have become increasingly popular, they still are not an option that many are presented with when they encounter health-related issues.

Financial restraints may also contribute to accessibility issues in the United States. Various private insurance plans such as Health Net, United Healthcare, and Aetna have covered acupuncture for many years (27). Some government-run programs including Medicare and the Veterans Administration

also added acupuncture to their benefits in 2020. However, many insurance companies do not employ acupuncturists, as three US states have not officially recognized acupuncture as a valid and effective treatment option, which makes it difficult or impossible to bill them for their services (27). Additionally, out-of-pocket expenses for such therapies may not be affordable to the general public, thus furthering this inaccessibility.

Countries such as Germany and Taiwan utilize acutherapies more than the United States. It is estimated that a third of German medical doctors utilize this therapy in their own practices (28). Another study based in Germany stated that acupuncture is the most prominent and popular complementary medicine treatment in the healthcare system (29). However, there is an association between the use of acupuncture and older age; this suggests that it may not be presented as a common option for many children. Financially, acupuncture has been reimbursed by German health insurance since 2007 (30). Similarly, acupuncture services are under the National Health Insurance in Taiwan, and there was a higher prevalence of acupuncture usage (11%) in 2011 compared to utilization in the United States (31).

Common acupoints used

In the included articles, some of the most frequently used acupoints include the Stomach 36 (ST-36), Pericardium 6 (PC-6), and Large Intestines 4 (LI-4), which were referenced in 33% of the articles (16, 24, 32). All three of the articles that referenced these acupoints compared them with sham acupuncture and found that these acupoints were positively correlated with the occurrence of vomiting and the severity of nausea more so than the control group, but two (Reindl et al., 2006 and Yeh et al., 2012) were unable to achieve a statistically significant outcome due to the limited number of participants. Another article found the need for antiemetic medication and occurrence of vomiting significantly lower in the intervention group than the control group (32). Other acupoints include five reflex points on the ear, in a form of auricular acupressure (14). However, these also led to unclear results due to the small study size. Finally, the last two studies used acupressure wristbands at the acupoint PC-6 but found that it was not more effective than placebo (33-34).

Responses to treatment and studies' limitations

In addition to evaluating the efficacy of acupressure and acupuncture, all six articles from high-income countries used a standard amount of antiemetic medication for all participants. Two of the articles demonstrated increased control of CINV from acupuncture and acupressure (24, 32). Another two of the articles found that acupressure was not more useful than the sham group (33-34). The last two articles noted that patients in the intervention group reported lower severity and occurrence of nausea and vomiting (14, 16). However, the findings were not statistically significant which is mostly due to the insufficient study size, thus not having enough statistical power to detect a statistical difference, if there was one. Based on the power calculation, 35 participants were needed in the trial by Reindl et al., but due to attrition, only five patients were followed through to the end of the study. In addition to both studies not having sufficient sample size to achieve the desired statistical power, some other possibilities include how both studies used self-reported questionnaires which are more prone to attrition, selection, and recall biases given the subjectiveness.

There may be multiple other reasons as to why acupuncture was not statistically effective in these two studies. For example, in the study by Yeh et al., the researchers had two groups (sham and intervention) in which they stimulated auricular acupoints in accordance with Dr. Huang's ear reflex theory for the intervention and sham groups (14). Auricular acupoints are rarely used to treat nausea and vomiting in the clinical setting. The acupoints in the intervention group included shenmen, sympathetic, cardia, stomach, and digestive subcortex (Table 1), which were known to treat nausea

and/or vomiting according to Dr. Huang's ear reflex theory (Table 2); whereas the sham group had acupoints that were not known to treat nausea and/or vomiting (14). Given the physiological pathways of the acupoint are unclear (Table 1), the statistically insignificant findings may have been due to the placebo effect in the sham acupressure group. For example, it may be difficult to blind participants during acupuncture research as the sensation of a needle is difficult to replicate (35). In the sham group, if participants were not properly blinded, they may have reported reduced nausea and vomiting because they believed they were receiving the intervention. This could have resulted in a small difference in the reduction of CINV between the sham and intervention groups, and given the insufficient sample size, there would not have been enough statistical power to detect such a small difference. Additional possibilities that may have resulted in statistical insignificance of the results are that the children's population may not be the most reliable as they may not be able to accurately recall the impact of the acupuncture. Whereas in the study by Reindl et al., since the acupuncturist was a human, results are subject to human errors. For example, placing the acupuncture needle in the wrong position or depth may cause the acupoint to not be stimulated properly, which would alter or affect the results (Table 2). Additionally, given the randomized study design, Reindl et al. did not conduct an Intent to Treat or a Mixed-Effect Model analysis to ensure findings were robust (16).

The timing that acuthery is administered could also impact its effectiveness. One study found that acupuncture performed 30 minutes before chemotherapy significantly reduces the frequency of CINV when compared to acupuncture performed after chemotherapy and no acupuncture at all (36-37).

Table 1. Physiological pathways and their associated acupoints

Acupoints	Neural/muscular/hormonal/neurotransmitter pathways
ST36	Studies have shown that electroacupuncture at ST-36 seems to mitigate nausea and vomiting through a complex vagovagal pathway in rats (17). Acupuncture stimulates the sensory nerves at the ST-36 acupoint which travel through afferent nerve fibers to stimulate the dorsal motor nucleus of the vagus nerve, which controls involuntary movements of the digestive tract (17). This may promote gastric motility, which in turn reduces nausea (17, 38). This is further supported by a vagotomy in the rats, which completely abolished the increase in gastric motility that was observed after electroacupuncture at ST-36 (17). While this study focused on rats as test subjects, there have been some studies that show that the vagus nerve is stimulated in acupuncture in humans as well (39-43). One study found that electroacupuncture at ST-36 stimulates the sciatic nerve, which causes signals to be transmitted to the vagus nerve, although the mechanism as to how this occurs is unknown (41). However, many articles that have made this claim are not peer-reviewed articles.
PC6	Though the literature is sparse regarding the acupoint PC-6, scientists have reported that the acupoint PC-6 has been shown to selectively activate areas of the cerebellum (the nodulus and uvula) that are specifically involved in vestibular control and alleviates symptoms of motion sickness and nausea (44-45). It has also been suggested that acupuncture at PC-6 facilitates the release of neurotransmitters which may desensitize responses of the chemoreceptor trigger zone or vomiting center in the medulla, thus resulting in decreased nausea and vomiting (45).

LI4*	The LI-4 acupoint is known to provide pain relief (46). However, based on non peer-reviewed literature, acupressure at the combination of both LI-4 and ST-36 seems to be effective for preventing nausea (47). Additionally, peer-reviewed literature suggests that acupuncture at both PC-6 and LI-4 acupoints alongside antiemetic drugs (in both the control and intervention group) reduced nausea intensity as well as postoperative nausea and vomiting (48). A similar study also found that acupuncture at PC-6 and LI-4 was more effective at reducing post-operative nausea and vomiting than acupuncture at PC-6 alone (49). Based on this information, one can hypothesize that the LI-4 acupoint is effective in combination with other acupoints (ST-36 and PC-6) but more research is needed on the effectiveness of LI-4 alone when treating nausea and vomiting.
CV12*	CV12 has often been used in conjunction with PC6 and/or ST36 when treating nausea. On its own, it has been known to rectify digestion-related issues, such as bloating, constipation, and vomiting.
Auricular acupoints ⁺	This group of acupoints (shenmen, sympathetic, cardia, stomach, digestive subcortex) was cited in Dr. Huang's ear reflex theory (50). One physiological pathway to experiencing CINV is through the interaction of emetic drugs with dopamine receptors in the chemoreceptor trigger zone. This activates the nucleus tractus solitarius, which can initiate the emetic response. Thus, it is possible that the stimulation of auricular acupoints will decrease the sensitivity of the dopamine receptors, thus decreasing the severity of the CINV.
BL20*	This acupoint has been traditionally used to treat digestion-related issues such as vomiting and emesis. It has been shown to decrease xylazine induced emesis in dogs.
SP6*	The SP6 acupoint is most commonly used to treat labor or menstrual related pains but it has also been shown to be effective in treating postoperative nausea and vomiting.
KD3*	This acupoint is usually used to treat sleep, energy, and weight irregularities. However, many articles that have made this claim are not peer-reviewed.

Note

*: There is no clear evidence on specific physiological pathways for the following acupoints but listed below are the conditions these acupoints are typically known to treat.

+: There is no publically available evidence on the specific physiological pathway for the following acupoints but listed are the conditions these acupoints are typically known to treat.

Table 2. Effectiveness of reducing CINV with acupuncture/acupressure versus conventional treatment

Study	Results	Acupoints	Timing of acuthery	Why findings may or may not have been effective
Yeh et al., 2012	Findings were not statistically significant	Auricular acupoints (shenmen,	The acupressure was given	There is no scientific evidence supporting Dr. Huang's ear reflex theory

	between the acupuncture group and sham acupuncture group, with a reduction in CINV in the intervention group.	sympathetic, cardia, stomach, digestive subcortex)	three times a day after receiving chemotherapy, as well as when participants felt nausea, for a total of seven days.	being effective in reducing nausea and vomiting. However, it is possible that these acupoints were unsuccessful in modulating the sensitivity of the dopamine receptors (See pathological pathway for auricular acupuncture in Table 1). Since acupressure was given after receiving chemotherapy, this could have contributed to the statistical insignificance because it might have provided more time for the acuthery to stimulate physiological pathways to reduce CINV (Table 1.)
Reindl et al., 2008	Findings were not statistically significant between the acupuncture and control group but found that acupuncture could be effective at reducing CINV.	Acupoints were chosen by the acupuncturist to tailor to the patients' needs, most commonly used acupoints were PC6, ST36, CV12, LI4	Acupuncture was applied before starting chemotherapy and offered at consecutive days during the chemotherapy.	ST36 and PC6 may not have been stimulated enough to have modulated the vagus nerve, vestibular system, and/or neurotransmitter activity (See pathological pathway for PC6 and ST36 acupoints in Table 1). Since the administrator of the acupuncture was a person, it was subject to human error, one of which could be misplacing the acupuncture needle close to the acupoint, thus causing the effects of the acupoints to be compromised. Although the acupuncture was administered before starting chemotherapy, the sample size was too small to detect any statistical significance between the two groups.
Ralston-Wilson, 2013	Findings were statistically significant and	ST36, LI4, KD3, SP6, PC6	Not available	ST36 and PC6 modulated the vagus nerve, vestibular system, and/or

	found that acupuncture decreased CINV.			chemotherapy trigger zone which reduced nausea and vomiting. LI4 was also effectively stimulated as it was used alongside PC6 and/or ST36. (See pathological pathway for PC6, ST36, and LI4 acupoints in Table 1.) Although the timing of acupuncture was not available, starting the acupuncture before chemotherapy may have also contributed to the results.
Gottschling et al., 2008	Findings were statistically significant between the acupuncture group and no acupuncture group, with a significant reduction in the need for antiemetics in the acupuncture group.	PC6, ST36, CV12, LI4	Acupuncture was given before starting chemotherapy and offered at consecutive days during the chemotherapy course based on the patient's demand.	ST36 and PC6 modulated the vagus nerve, vestibular system, and/or chemotherapy trigger zone which reduced nausea and vomiting. LI4 was also effectively stimulated as it was used alongside PC6 and/or ST36. (See pathological pathway for PC6, ST36, and LI4 acupoints in Table 1.) Starting the acupuncture before chemotherapy may have also contributed to the results as it might have provided more time for the acuthery to stimulate physiological pathways to reduce CINV (Table 1.)
Dupuis, 2018	Findings were not significant; acupressure wristbands did not reduce CIN in the acute or delayed phases.	PC6	Wristbands were worn starting at least 30 minutes before chemotherapy and continuously throughout	PC6 wristbands may not have exuded enough pressure to stimulate the pathways that the PC6 acupoint usually stimulates, regardless of when they were used. (See pathological pathway for PC6 in Table 1.) According to Sea-band

			<p>the entire chemotherapy course and up to seven days after.</p>	<p>Australia, the brand of acupressure wristband that was used, the wristbands take 2-5 minutes to create an impact. Since the wristbands were worn before chemotherapy, they should have become effective during chemotherapy, further suggesting that the wristbands did not properly stimulate the physiological pathway of PC6 (51). Lastly, an insufficient sample size may have contributed to the insignificance of the findings because the authors did not enroll the minimum number of participants needed in each group.</p>
<p>Jones et al., 2008</p>	<p>Findings were not significant; acupressure wristbands did not cause a significant reduction in nausea or vomiting.</p>	<p>PC6</p>	<p>Wristbands were worn starting before chemotherapy and they were taken off after the conclusion of chemotherapy.</p>	<p>PC6 wristbands may not have exerted enough pressure to stimulate the pathways that the PC6 acupoint usually stimulates, regardless of when they were used. (See pathological pathway for PC6 in Table 1.) According to Sea-band Australia, the brand of acupressure wristband that was used, the wristbands take 2-5 minutes to create an impact. Since the wristbands were worn before chemotherapy, they should have become effective during chemotherapy, further suggesting that the wristbands did not properly stimulate the physiological pathway of PC6 (51). Lastly, an insufficient</p>

				sample size may have contributed to the insignificance of the findings because there is a possibility that the authors did not enroll the minimum number of participants, given that they did not include a minimum required sample size.
Varejão et al., 2019	Findings were statistically significant, showing that laser acupuncture was effective at relieving nausea and vomiting	PC6, LI-4, ST-36, BL-20, and SP-6	The laser was applied a few minutes before the start of chemotherapy.	ST36 and PC6 modulated the vagus nerve, vestibular system, and/or chemotherapy trigger zone which reduced nausea and vomiting. LI4 was also effectively stimulated as it was used alongside PC6 and/or ST36. (See pathological pathway for PC6, ST36, and LI4 acupoints in Table 1.) Starting the acupuncture before chemotherapy may have also contributed to the results as it might have provided more time for the acuthery to stimulate physiological pathways to reduce CINV (Table 1.)
Abusaad et al., 2015	Findings demonstrated that acupuncture significantly decreased nausea, vomiting, and retching.	PC6	Participants were instructed to perform acupuncture before starting chemotherapy and at least three times daily afterward.	PC6 modulated the vestibular system, and/or chemotherapy trigger zone which reduced nausea and vomiting. (See pathological pathway for the PC6 acupoint in Table 1.) Starting the acupuncture before chemotherapy may have also contributed to the results as it might have provided more time for the acuthery to stimulate physiological pathways to reduce CINV (Table 1.)

CINV in children in LMICs

Twenty-five percent (two out of eight) of the articles included in this review were published in LMICs. Of these articles, one was published in Egypt while the other was published in Brazil.

Accessibility of acupuncture/acupressure and how it's portrayed as an option for children with CINV

The practice of traditional Chinese medicine in Brazil, including acupuncture and acupressure, began with the arrival of Chinese immigrants in the early 1800s (52). Since then, many immigrants and native Brazilians have participated in this treatment. In fact, it is believed that there are approximately 160,000 acupuncturists in Brazil according to the Federation of Acupuncturists of Brazil (52). Despite the abundance of professional acupuncturists in Brazil, not all citizens utilize their services. Wealthy individuals, or those who had a higher education and a private health plan, are more likely to use integrative and complementary practices such as acupuncture and acupressure (53). There is limited data available on acupressure regarding the utilization, the number of certified individuals, and the number of facilities that offer acupressure services, as acupuncture is much more commonly practiced in Brazil. In terms of financial accessibility, acupuncture is included in the health insurance provided by the Sistema Único de Saúde, Brazil's national health service (54). However, it is rarely used compared to its usage with private health insurances (54).

In Egypt, there is only one acupuncture clinic in public hospitals as of 2016 (55). Although an increasing number of doctors have become more interested in acupuncture, there is no formal acupuncture educational training or legal regulations on its practice, which means there is no uniform way to learn or practice acupuncture (55). Additionally, it is not covered by medical insurance, furthering its inaccessibility to civilians (56). While there are numerous research articles published on acupressure and its effects in Egypt, there are no statistics regarding the prevalence of acupressure.

Common acupoints used

One hundred percent (two of two) of the articles from LMICs referenced the PC-6 acupoint in their intervention group, located on the inside of one's wrist (57-58). However, one article also referenced the LI-4, ST-36, BL-20, and SP-6 acupoints (57). By referencing only one acupoint, one can determine the efficacy of that acupoint in treating CINV. However, using multiple acupoints allowed acupuncturists to individualize the treatment plan according to the patient, which may lead to better results.

Responses to treatment

In addition to evaluating the efficacy of acupressure and laser acupuncture, all articles from LMICs used a standard level of antiemetic medication for all participants. The responses to the acupressure were positive in both studies. Researchers of the Brazil study found laser acupuncture to be effective at relieving nausea five days after chemotherapy as well as vomiting two and three days after chemotherapy (57). Researchers of the Egypt study found that acupressure on the PC-6 point significantly reduced nausea, retching, and vomiting in the participants (58).

A direct comparison of high vs. LMICs: acupuncture/acupressure for children with CINV Accessibility

Acupuncture and acupressure are becoming increasingly popular around the world, but of the countries included in this review, the United States is most prominent. The accessibility of acupuncture in Taiwan suggests that Asian countries who are in close geographic proximity to China are more likely to use traditional Chinese medicine such as acupuncture and acupressure. Similarly, Brazil, which has had many Chinese immigrants since the 1800s, also has a higher prevalence of acupuncture (52).

Additionally, Germany seems to have also deeply implemented this therapy into their healthcare system despite its more westernized culture. The only country that had significantly poor access to acupuncture is Egypt. However, the increasing number of studies published in Egypt suggests that acutherapies may become more widespread in the future.

Financially, four of the five countries (USA, Germany, Taiwan, Brazil) include acupuncture in the public medical insurance. However, in the US and Brazil, acupuncture is more commonly used in private medical insurance plans. In both these countries, financially able citizens are more likely to use acupuncture compared to marginalized and vulnerable populations, those living at or below the poverty threshold, who utilize other complementary therapies. Given both private and public medical insurances cover acupuncture services, those with private insurance utilize these services more often (54). This could be due to them having more knowledge and understanding of the benefits of acupuncture. Whereas vulnerable populations with public insurance may not be as knowledgeable of the benefits of acupuncture or that it is even covered by their insurance. Overall, while acutherapies seem to be more popular amongst the upper-class, it is becoming more widespread around the world.

Acupoints used

The most popular acupoint for treating CINV in children is the Pericardium-6 (PC-6) acupoint, which was referenced in five research articles (16, 24, 32, 57-58). However, there were various other acupoints that were commonly referenced such as Large Intestine-4 (LI-4) and Stomach-36 (ST-36), which were included in four articles (16, 24, 32, 55). These acupoints are also often referenced in studies on the efficacy of acupuncture on CINV in adults and seem to have a positive impact in preventing and minimizing the effects of CINV (59-60). The PC-6, ST-36, and LI-4 acupoints are also commonly used to treat nausea and vomiting even without the presence of chemotherapy (61). Thus, it makes sense that these acupoints would be effective for treating CINV given that they are already used for treating nausea and vomiting.

Responses to treatment and studies' limitations

Of the eight studies included in this review, four studies found acutherapy to be effective at preventing nausea and vomiting (24, 32, 57-58). Two studies saw positive impacts of acutherapy on CINV outcomes but due to their small study sizes and perhaps an inability to properly stimulate the acupoints (Table 2), these findings were not statistically significant (14, 16). Furthermore, two studies found acutherapy to not be more effective than the placebo in preventing CINV (33-34). These studies both used acupressure wrist bands with acupoint PC-6. The PC-6 acupoint is commonly used amongst the other studies and has been shown to have beneficial effects in the prevention and treatment of CINV (16, 24, 32, 57-58). Thus, it can be inferred that acupressure wrist bands may not have exerted enough pressure to stimulate the PC-6 acupoint (33-34).

Evaluation of the neural pathways involved in triggering nausea and vomiting

Steps of neural pathway of acupoint

Studies have shown that electroacupuncture at ST-36 seems to mitigate nausea and vomiting through a complex vagovagal pathway in rats (17). Another study found that electroacupuncture at ST36 stimulated the sciatic nerve which can send signals to the vagus nerve (43) (Table 1).

Though the literature is sparse regarding the acupoint PC-6, scientists have reported that the acupoint PC-6 is involved in vestibular control and modulating the chemotherapy trigger zone, which may result in decreased nausea and vomiting (Table 1).

While the LI-4 acupoint is known to provide pain relief (46), there have not been many studies evaluating the efficacy or physiological mechanism of the LI-4 acupoint alone on treating nausea and vomiting (Table 1). However, there is evidence that the LI-4 acupoint, when combined with PC-6 or ST-36, can exacerbate their effects in reducing CINV (Table 1) (47-49).

Limitations

One of the most prominent limitations of this review is how little research has been conducted on the efficacy of acupoint therapy for CINV in children. To minimize the impact of this, literature was searched across multiple databases, such as the National Center for Biotechnology Information (NCBI) and Google Scholar for articles that may be available on one database and not the other. Additional literature was found by reading cited articles that were relevant to this topic.

The literature is also limited as it relates to the general accessibility of acupoint therapy in the research setting (only one article described the accessibility). To minimize the impact of this, other literature was explored to find statistics on the accessibility of acupoint therapy in relevant countries that was not provided in the literature. However, while this was able to provide a general idea of the prevalence of acupoint therapy, it may not accurately reflect the situation in the research setting.

Finally, there was not a lot of publicly available literature on certain acupoints (auricular acupoints) and their mechanisms as well as not enough peer-reviewed literature on how some acupoints are stimulated to reduce CINV. To mitigate this, non peer-reviewed articles were cited when the information was consistent across multiple sources. Additionally, hypotheses for the physiological pathway of the auricular acupoints were created based on the publicly available literature.

Future research

Future research should first explore the accessibility of acupoint therapy in the research setting more, as it provides insight into the prevalence and the standardization of this therapy. Second, researchers should consider focusing on specific acupoints to determine the efficacy of each point, instead of using a variety of acupoints. Third, the physiological pathways and mechanisms of how stimulating acupoints such as LI-4, CV-12, and the auricular acupoints would reduce nausea and vomiting should be explored and researchers should be sure to properly stimulate each acupoint to achieve the desired effect. Therefore, to incorporate the above recommendations, researchers would need to conduct more randomized control trials with larger patient populations to ensure sufficient statistical power to identify differences if they exist, and the impact of the placebo effect, if any, should be explored. An example of a randomized control trial to establish potential causal relationships is provided below.

Proposed clinical trial

The proposed randomized control trial will include participants between the ages of 5 and 18 who were diagnosed with any type of cancer and have a history of experiencing CINV. Anyone with a history of acupuncture will be ineligible because it would be more difficult to blind them with sham acupuncture if they experienced true acupuncture before. Additionally, there may be lasting effects from previous acupuncture which could impact the trial results.

The trial will start in the summer of 2025 and last for half a year. Participants will be enrolled from The Hospital for Sick Children in Ontario, Canada from May 1, 2025 to August 31, 2025 or when the number of participants reaches 120. Based on sample size calculations and to achieve 80% statistical power, the study will need a total of 90 children with 30 children in each arm. The study aims to enroll 120 participants, which is 30 children more than the minimum required, to adjust for those lost

to follow-up. This will minimize the impact of attrition bias and ensure good internal validity of the study.

The trial will include three arms: pill only, pill+sham acupuncture, and pill+acupuncture, where pill denotes the antiemetics to be used as standard care. The control group will receive the standard of care, which is only antiemetics (no acupuncture or sham acupuncture is provided to these participants). The pill+sham group will receive antiemetics in conjunction with sham acupuncture. Lastly, the pill+acupuncture group (the true intervention group) will receive antiemetics in conjunction with acupuncture. Participants will receive their allotted treatment for three successive rounds of chemotherapy. Nausea and vomiting will be monitored through self-reported questionnaires and a daily journal. Everyday after the intervention, participants will journal about their symptoms, including a tally of the daily occurrence of vomiting, and likert scales for the severity of nausea (from 0-10), frequency of nausea (1x/day, 2x/day, 3x/day, 4x/day, 5x+/day), and duration of nausea (0-2 hours, 2-4 hours, 4-6 hours, 6-8 hours, 8+ hours). One week post intervention, participants will complete electronic surveys at home when they can refer to their journal. This will include all the information participants have recorded in their journal. By having participants keep daily journals, this minimizes potential recall bias in this study.

Acupuncture will be performed by a single licensed acupuncturist to ensure standardized acuthery is administered and reduce human error. Sham acupuncture will also be performed by the same acupuncturist, by inserting an acupuncture needle into a location that, according to Chinese Traditional Medicine, will not have any effect on nausea and vomiting. ST-36 and PC-6 will be the two acupoints targeted because these are known to alleviate CINV. By focusing on these two acupoints, if the intervention (pill + acupuncture) is effective, the acupoints will reflect that given its sensitivity to acupuncture. Whereas, if the intervention is ineffective, that will also be revealed in both the intervention group and sham acupuncture + pill group.

Based on the results of the trial, each group will receive a 0 or +1, where 0 represents a baseline effectiveness and +1 represents a significantly greater reduction in CINV. The pill+sham acupuncture group will reveal whether there is evidence of the placebo effect and whether this has any impact on the results of the trial. For example, if there is evidence of the placebo effect, participants might report a reduction in CINV and this reduction may mimic the true reduction seen in the pill+acupuncture group. Thus, this will result in insignificant findings in reduction of CINV between the two intervention groups, further supporting evidence of the placebo effect.

The proposed study will be reviewed and approved by The Hospital for Sick Children's ethics committee and the hospital's Institutional Review Board (IRB).

Table 3. Anticipated results of proposed randomized control trial

	Pill only	Pill + sham acupuncture	Pill + acupuncture
Frequency of vomiting	0	0	+1
Frequency of nausea	0	0	+1

Duration of nausea	0	0	+1
Severity of nausea	0	0	+1

Note: 0 denotes a baseline effectiveness

The anticipated results in Table 3 suggest that acupuncture used in conjunction with antiemetics is the most effective treatment. Whereas, antiemetics and sham acupuncture had no statistical difference from the antiemetics only group, which indicates that the placebo effect has no impact on the reduction of CINV. These potential findings suggest that sham acupuncture is an appropriate control for future trials concerning acupuncture, given it is not possible to use a control group where participants are given acupuncture only because it is unethical, and CINV and that acupuncture does effectively mitigate CINV. The results from this study will allow researchers/clinicians to implement evidence-based interventions to reduce CINV in children.

Conclusion

Given the evidence provided in the trial studies, acupressure and acupuncture may be effective options for the prevention and treatment of CINV in children. More specifically, acupoints PC-6, ST-36, and LI-4 were effective in controlling CINV whereas auricular acupoints were not. However, acupressure wristbands that target the PC-6 acupoint were shown to be ineffective based on findings from two studies (33-34). While acupuncture is becoming increasingly popular around the world as an alternative medicine, there are still accessibility barriers such as insurance coverage that prevents people from using this therapy. Additionally, while there is literature on how acupuncture at PC-6 and ST-36 reduce CINV, there remains many acupoints such as LI-4, CV-12, and auricular acupoints that do not have an outline of their physiological pathways. Thus, future research should take into consideration the accessibility of acutheraPy to reveal its practical implications as well as focus on specific acupoints to determine their effectiveness. Researchers should also conduct more trials of the physiological pathways of specific acupoints. Research studies with more participants are needed to have adequate power to detect a statistically significant difference, if one exists, which will determine whether these therapies are truly effective in prevention and treatment of CINV in children. Furthermore, most of the existing literature incorporates the acutheraPy before chemotherapy, which resulted in statistically significant findings. However, more research that focuses on the time in which acutheraPy is administered is needed. This is because the trials that provided acutheraPies after chemotherapy found that the acutheraPy was less effective, indicating that time may be a critical factor in determining effectiveness of acutheraPies.

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Abbreviations

CINV	Chemotherapy-induced nausea and vomiting
PC-6	Pericardium 6
LI-4	Large Intestines 4
ST-36	Stomach 36
TCM	Traditional Chinese medicine
LMIC	Low- and middle-income countries

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