Review

Neuropsychobiology

Neuropsychobiology 2018/2019;78:59–69
DOI: 10.1159/000499136

Received: January 4, 2019
Accepted after revision: February 26, 2019
Published online: April 12, 2019

# Diagnostic Utility of Sodium Lactate Infusion and $CO_2$-35% Inhalation for Panic Disorder

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**Keywords**
Panic disorder · Diagnostic testing · Sodium lactate infusion · $CO_2$ inhalation

**Abstract**
Laboratory measures have played an integral role in diagnosing pathology; however, compared to traditional medicine, psychiatric medicine has lagged behind in using such measures. A growing body of literature has begun to examine the viability and development of different laboratory measures in order to diagnose psychopathologies. The present review examines the current state of development of both sodium lactate infusion and $CO_2$-35% inhalation as potential ancillary measures to diagnose panic disorder (PD). A previously established 3-step approach to identifying laboratory-based diagnostic tests was applied to available literature assessing the ability of both sodium lactate infusion or $CO_2$-35% inhalation to induce panic attacks in PD patients, healthy controls, and individuals with other psychiatric conditions. Results suggest that across the literature reviewed, individuals with PD were more likely to exhibit panic attacks following administration of sodium lactate or $CO_2$-35% compared to control participants. The majority of the studies examined only compared individuals with PD to healthy controls, suggesting that these ancillary measures are underdeveloped. In order to further determine the utility of these ancillary measures, research is needed to determine if panic attacks following administration of these chemical agents are unique to PD, or if individuals with related pathologies also respond, which may be indicative of transdiagnostic characteristics found across disorders.



## Introduction

Laboratory tests have been essential in modern medicine, and have allowed for accurate diagnosis and differentiation from other related pathologies [1]. In the absence of objective laboratory-based testing, diagnosis is susceptible to observer bias as well as to judgement error. Much like traditional medicine, psychiatric research has identified biological and laboratory measures that can differentiate healthy from nonhealthy individuals, such as abnormal P300 in schizophrenia and potentiated error-related negativity in anxiety disorders [2, 3]. Despite the potential utility of using biological indices to detect



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psychiatric illness, the field has lagged behind traditional medicine in adopting these measures [4]. Largely, these laboratory tests have either not been developed into diagnostic tools (e.g., P300 evoked response in schizophrenia) or have been prematurely dismissed before the validity of the measures can be established (e.g., quantified electroencephalogram). Currently, psychiatric assessment and diagnostic procedures are time consuming, and are contingent upon behavioral and self-report measures, both of which can be affected by self-report bias and underreporting, as well as poor patient insight [5–8]. These limitations found in psychiatric assessment are less prevalent in other fields of medicine and further emphasize the need to integrate laboratory measures into the assessment processes in psychiatric medicine.

*Three-Step Approach for Developing Ancillary Diagnostic Measures*

By incorporating more objective laboratory measures, researchers and practitioners may be able to help the field move forward as diagnosis in psychiatry remains the major limiting step in biological research and treatment studies [9]. In recent years, researchers and practitioners have advocated that biological and laboratory measures should be integrated into the diagnostic processes for illnesses. A series of publications have called for a 4-step approach to help bridge this gap and integrate biological measures into assessment and diagnosis [4, 10, 11]. The original 4-step approach was subsequently modified to the currently proposed 3-step approach based on peer and grant reviewers' feedback. Both the 4-step and the 3-step approaches are consistent with guidelines for creating clinical usefulness of diagnostic tests [12] as well as criteria set by STARD (the Standard for Reporting Diagnostic Accuracy studies) [13, 14]. In the 3-step approach, steps 1 and 2 of the 4-step approach were expanded to include 2 substeps each [1].

In the 3-step approach (Table 1), step 1a calls for a biological variable to be observed and replicated as deviant compared to healthy controls in a particular patient population. After this deviant response is reliably observed, step 1b calls for measures of sensitivity and specificity of the biological variable to be obtained from ROC (receiver-operating characteristic) curves [15], which allows researchers to determine "cut points" of the biological variable (e.g., individuals above or below a certain score meet criteria for diagnosis). Step 2a is used to help determine the clinical usefulness of the specific biological variable by testing whether or not individuals with related pathologies also exhibit the biological variable. This is an important point, as some pathologies share diagnostic criteria and are common rule-outs for one another (e.g., bipolar disorder with psychotic features and schizophrenia). Determining if a biological variable is specific to one pathology (e.g., panic disorder [PD] and not other anxiety disorders), the test is then likely to contribute to the diagnostic process by suggesting that the variable can appropriately discriminate among related pathologies.

Similar to step 1b, step 2b is used to determine sensitivity and specificity where a "best estimate diagnosis" is reached by agreement among a number of experts relying on multiple sources of information and with a standardized scale with demonstrated validity and reliability [16]. Furthermore, step 2b is used to examine heterogeneity of the disorder of interest, to determine if there are subgroups of individuals within a diagnostic category who do not exhibit the biological variable. Finally, step 3 defines the clinical application of the test and helps to standardize the technique used in large multicenter clinical trials and develop large normative databases that can eventually be used for comparison with an individual's data (see Arfken et al. [1] for a complete review of the 3-step approach).

*Previous Use of the 3-Step Approach*

Previous research has documented that this 3-step approach (formerly 4 steps) can be useful in determining the stage of development of a biological finding into a clinically useful laboratory test [4]. Previous reports have investigated the extent to which both resting state α and spectral EEG abnormalities can be used as diagnostic measures for attention deficit hyperactive disorder and schizophrenia, respectively [4, 17]. More recently, this 3-step approach has been used to investigate whether or not polysomnographic abnormalities and dexamethasone/corticotropin-releasing hormone should be investigated further as potential diagnostic measures for major depressive disorder (MDD) [1, 18]. Collectively, these reports suggest the aforementioned measures could be diagnostically useful; however, additional research is needed to compare results to related pathologies and create clinical norms for diagnosing. While initial literature has identified attention deficit hyperactive disorder, MDD, and schizophrenia as diagnoses with potential biological indices suggestive of disease, other psychiatric illnesses with established biological abnormalities should consider adopting the 3-step approach to further determine the utility of biological measures in psychiatry and psychology.

**Table 1.** Three-step approach

| Step | Design | Purpose |
|---|---|---|
| 1a | Target group vs. healthy controls | Demonstrate that target group responds |
| 1b | Target group vs. healthy controls | Establish sensitivity and specificity to proposed measure |
| 2a | Target group vs. appropriate comparison group | Demonstrate that comparison groups do not respond |
| 2b | Target group vs. appropriate comparison group | Establish sensitivity and specificity to proposed measure and identify subgroups of the target group that does not respond |
| 3 | Steps 1a–2b but across multiple facilities | Demonstrate that the target group responds across settings and standardize assessment procedures |

*The Current Study*

The purpose of the current report is to examine in a similar manner the status of development of sodium lactate infusion and 35% carbon dioxide ($CO_2$-35%) inhalation as diagnostic measures for PD. In addition to the diagnostic overlap with other pathologies, PD is relatively common among the public, with 12-month and lifetime prevalence of PD in the United States estimated at 2.7 and 4.7%, respectively [19, 20]. Compared to other psychiatric illnesses, PD is unique in that chemical agents referred to as panicogens can provoke panic attacks, the hallmark symptoms of PD. Both $CO_2$-35% and sodium lactate are considered panicogens, which may make them viable diagnostic tools for PD [21].

Determining whether or not these 2 panicogens can aid in diagnosing PD is an important step for researchers and physicians, as symptoms of PD have diagnostic overlap with other related psychiatric illnesses (e.g., social anxiety, generalized anxiety disorder, and specific phobia), unrelated medical conditions (e.g., asthma and myocardial infarction), as well as diagnostic specifiers for other psychiatric illnesses (e.g., posttraumatic stress disorder [PTSD] with panic attacks). If these 2 panicogens can discern PD from other pathologies, including pathologies where panic attacks or panic-like symptoms may be present, researchers may be able to understand the mechanisms that make this disorder distinct from others, and physicians may be able to more accurately and quickly diagnose patients with PD. Additionally, if there are no differences in panic responses in individuals with PD and related pathologies, a shared, *transdiagnostic* factor may be responsible for the panic attack following sodium lactate or $CO_2$-35% administration across the diagnoses. In either case, clarifying the role these chemical agents may play in patients with PD or related pathologies, and healthy controls is important, as psycho- and pharmacotherapies are effective in treating PD, which suggests that if individuals with PD can be identified early and accurately, their symptoms can be ameliorated in most cases [22, 23].

In summary, the present study examined relevant literature where sodium lactate or $CO_2$-35% were administered to individuals with PD, as well as comparison groups to determine (1) if individuals with PD respond differently to comparison groups, and (2) to assess the state of development of these ancillary measures based on the 3-step approach. We predicted that individuals with PD would be more likely to exhibit panic attack following administration of sodium lactate and $CO_2$-35% compared to control participants, and that the majority of existing literature would compare individuals with PD to healthy controls.

## Materials and Methods

*Inclusion and Exclusion Criteria*

Studies with the objective of comparing the results of the sodium lactate infusion test in individuals with PD and healthy control subjects or other patient groups, as well as studies comparing the $CO_2$-35% inhalation test results in individuals with PD and healthy control subjects or other patient groups were initially selected. While previous studies have examined $CO_2$ concentrations as low as 5% [24] and as high as 50% [25], articles that used a concentration of 35% were selected for the present study due to the number of available and relevant articles. Similarly, sodium lactate was selected over other panicogenics, such as L-DOPA and caffeine, due to the number of available and relevant papers. These studies were identified and categorized according to the 3-step approach. While no reviews were included, relevant review articles were used as sources for potential additional relevant experimental studies [26–29]. The following information was extracted from each paper: number of PD subjects,

number of control subjects, number of PD subjects that reacted to sodium lactate infusion and $CO_2$-35% by developing a diagnosable panic attack, and control subjects that reacted similarly to sodium lactate infusion and $CO_2$-35%. If a paper did not contain these pieces of information or did not clearly state these facts at any point, they were excluded.

*Sodium Lactate Infusions*

Studies not including a PD group alongside a control group were excluded. Review articles were not considered eligible for inclusion if no new data were provided. We also excluded the studies assessing the value of the sodium lactate only in predicting treatment response (i.e., PD treatment efficacy or relapse prediction). While prediction of treatment response is undoubtedly a very important goal of laboratory testing, we elected to adopt this exclusion for 2 reasons. First, the focus of the current review is on diagnosis. Secondly, our preliminary review of this literature suggested the number of reports using the exact same methodology (including testing prediction of response) was not adequate for a meaningful meta-analysis.

*CO2-35% Inhalation*

Similar to sodium lactate infusion studies, studies not including a PD group alongside a control group were excluded. Studies utilizing only $CO_2$-35% in PD patients without controls, and studies that used 5%, 7%, or any other concentration of $CO_2$ or any other methodology except for the proposed $CO_2$-35% vital capacity inhalation were also excluded. We also excluded the studies assessing the value of $CO_2$ inhalation only in treatment response (i.e., PD treatment efficacy or relapse prediction), although the pretreatment inhalation-induced panic rates were added to our data if a control group was included.

*Literature Search*

The review of the literature on this topic aimed at including all the published articles that could be identified as compatible with 1 or more of the 3 steps from the aforementioned 3-step approach. PubMed was the database used, as PsychInfo yielded very few articles that were not available in PubMed. The search strategy was seeking articles with a combination of the following 2 main groups of keywords, using "AND" connector. The first group comprised the articles, which had the following keyword/phrase: "Panic disorder". The second group encompassed the articles indexed under MeSH major topic of these keywords/phrases using "OR" connector: "lactate infusion", "sodium lactate infusion." The third group consisted of articles identified using the following keywords: "carbon dioxide inhalation," "$CO_2$ inhalation," and "hypercapnia." The search results were subsequently narrowed by limiting them to human subjects and English language. All the abstracts were reviewed for relevance to our study objective, and, where appropriate, the full texts were reviewed for further clarification. Reference lists of the full-text articles were also reviewed for potential addition of articles which were not initially identified. Articles that used the same samples were excluded, except when the articles used different comparison groups (e.g., same PD sample but different control samples).

The initial step in the literature review extracted 3 groups of articles. The first group consisting of all articles on "panic disorder" yielded 8,503 entries. The second group of all articles indexed under the "lactate infusion" OR "sodium lactate infusion" topics produced 2,110 entries. The third group of articles consisted of all articles containing "carbon dioxide inhalation" OR "$CO_2$ inhalation" OR "hypercapnia" topics produced 7,681 entries. Using the "AND" connector between the first and second group, 111 articles were identified. Review of the 111 abstracts and of the full texts, as well as review of included reference lists, yielded 22 articles meeting all criteria for the study for sodium lactate infusion. This progressive elimination process is depicted graphically in Figure 1. The full texts of the 22 included articles were thoroughly reviewed to assess the characteristics of each study. They were subsequently categorized based on the criteria for each of the 3 steps in the progression. Using the "AND" connector between the first and third group ($CO_2$ inhalation), 187 articles were identified. Review of the 187 abstracts and of the full texts, as well as review of included reference lists, yielded 16 articles meeting criteria for the study, as depicted in Figure 2.

## Results

*Sodium Lactate Infusion*

As seen in Table 2, 20 of the 22 studies that used sodium lactate infusion were classified as step 1a (i.e., comparing target patient group to healthy control subjects). From this alone, it can be suggested that sodium lactate infusion as a diagnostic test for panic disorder remains underdeveloped. Because of this, analyses comparing panic attacks in PD versus other pathologies were not examined. A single logistic regression was conducted to predict panic attacks as a dichotomous outcome following sodium lactate infusion, with PD status as a predictor variable.

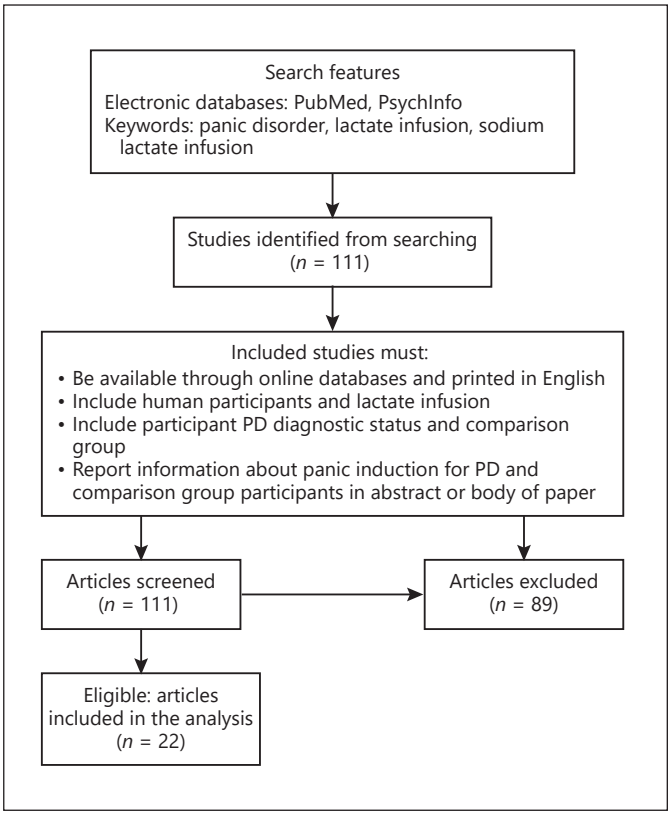


**Fig. 1.** Flowchart depicting selection and inclusion of lactate infusion studies.

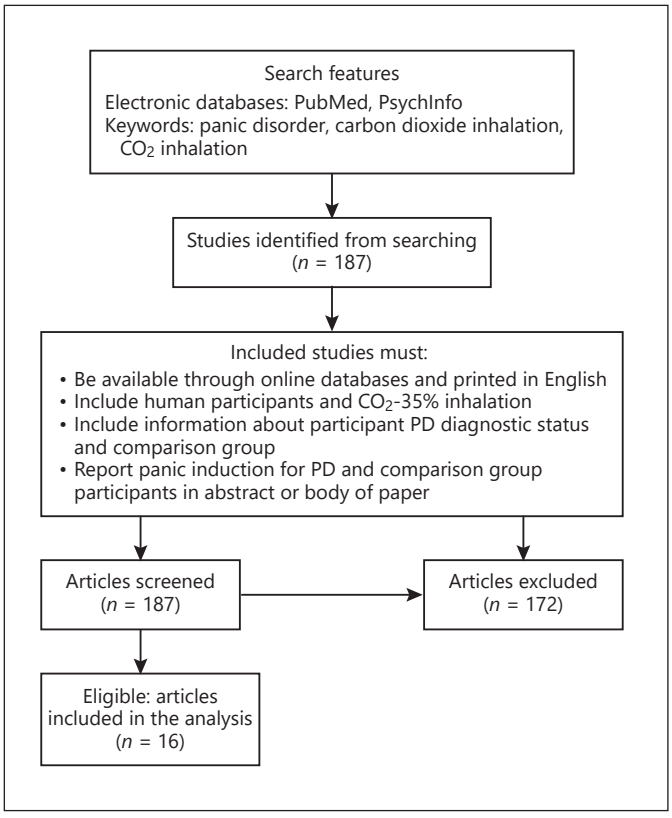


**Fig. 2.** Flowchart depicting selection and inclusion of $CO_2$-35% inhalation studies.

A test of the full model against a constant-only model was statistically significant, revealing that panic attacks following sodium lactate infusion can reliably distinguish between individuals with and without PD ($\chi^2 = 306.34$, $p < 0.001$, $\varphi = 0.568$, df = 1). A Nagelkerke's $R^2$ value of –0.434 indicates a moderately strong relationship between PD status and panic attacks following sodium lactate infusion, with a prediction success of 74.2% (97.3% for PD and 56.9% for control). An observed Wald statistic of 121.58 demonstrated that PD status made a significant contribution to prediction ($p < 0.001$), with an Exp ($B$) value of 48.01, revealing that individuals with PD are 48.01 times more likely to have a panic attack following sodium lactate infusion than individuals without PD.

It is worth mentioning that when the severity of panic attacks was taken into account [30], PD patients with attacks less frequent than once per month did not differ from healthy controls. Two studies compared PD patients to other patient control groups (step 2a). Facchinetti et al. [31] compared PD patients to patients with the premenstrual syndrome (PMS). They reported that panic attacks following sodium lactate infusion were equal among individual PMS patients regardless of comorbid diagnoses. They did not directly compare PMS patients with PD to PMS patients without PD, but the data suggest that sodium lactate infusion did not differentiate those with and without PD within the PMS group. This suggests a common variable across both PD and PMS, which predisposes individuals to panic attacks following administration of a sodium lactate solution.

Targum [32] compared PD patients to MDD patients with and without a history of panic attacks, as well a healthy control group. In this study, patients with PD and MDD with a history of panic attacks showed significant panicogenic response to sodium lactate infusion. These data support a possible differential diagnostic role for sodium lactate infusion in diagnosing PD. Nonetheless, the most value would be obtained by comparing different disorders like PTSD, specific phobia, or social or generalized anxiety disorders. We were unable to identify any studies addressing this differential diagnostic issue.

**Table 2.** Three-step designation of sodium lactate-induced panic studies reviewed

| Study | PD: control | PD panic: control panic | Step |
|---|---|---|---|
| Otte et al. [63], 2002 | 8:8 | 7:1 | 1a |
| Dager et al. [64], 1999 | 15:10 | 12:0 | 1a |
| Coplan et al. [65], 1998 | 170:44 | 101:1 | 1a |
| Bisaga et al. [66], 1998 | 8:6 | 6:0 | 1a |
| Peskind et al. [67], 1998 | 8:7 | 6:0 | 1a |
| Dager et al. [68], 1997 | 13:10 | 10:0 | 1a |
| Seier et al. [69], 1997 | 10:10 | 7:2 | 1a |
| George et al. [70], 1995 | 20:14 | 15:0 | 1a |
| Kellner et al. [71], 1995 | 10:10 | 7:2 | 1a |
| Dager et al. [72], 1994 | 8:8 | 3:0 | 1a |
| Facchinetti et al. [31], 1992 | 9:16 | 8:2 | 2a |
| Targum [30], 1991, part 1 | 12:12 | 9:0 | 1a |
| Targum[30], 1991, part 2 | 14:12 | 0:0 | 1a |
| Targum[32], 1990 | 17:12 | 11:0 | 2a |
| Hollander et al. [73], 1989 | 38:16 | 25:0 | 1a |
| Papp et al. [74], 1989 | 12:8 | 5:0 | 1a |
| George et al. [75], 1989 | 22:8 | 9:0 | 1a |
| Aronson et al. [76], 1989 | 9:9 | 9:0 | 1a |
| Gorman et al. [77], 1988 | 31:13 | 18:1 | 1a |
| Stewart et al. [78], 1988 | 10:5 | 6:0 | 1a |
| Liebowitz et al. [79], 1984 | 43:20 | 31:0 | 1a |
| Fyer et al. [80], 1984 | 33:6 | 22:0 | 1a |

PD panic refers to the number of participants in each study with panic disorder that exhibited panic attack symptoms; control panic refers to the number of participants in control conditions that exhibited panic attack symptoms.

**Table 3.** Three-step designation of $CO_2$–35% inhalation-induced panic studies reviewed

| Study | PD: control | PD panic: control panic | Step |
|---|---|---|---|
| Schutters et al. [36], 2012 | 16:16 | 12:03 | 2a |
| Niccolai et al. [38], 2008 | 11:11 | 6:01 | 1a |
| Alkin et al. [81], 2007 | 24:12 | 10:02 | 1a |
| van Duinen et al. [82], 2007 | 16:16 | 13:04 | 1a |
| Perna et al. [83], 2004 | 14:14 | 11:02 | 1a |
| Ponto et al. [84], 2002 | 14:12 | 12:03 | 1a |
| Coryell and Arndt [85], 1999 | 12:31 | 4:01 | 1a |
| Caldirola et al. [33], 1997 | 16:16 | 11:09 | 2a |
| Perna et al. [39], 1995 | 20:20 | 11:01 | 2a |
| Perna et al. [35], 1995 | 23:23 | 12:00 | 2a |
| Perna et al. [86], 1995 | 10:07 | 7:00 | 2a |
| Perna et al. [34], 1995 | 43:43 | 20:01 | 1a |
| Perna et al. [87], 1994 | 71:44 | 34:02:00 | 1a |
| Papp et al. [88], 1993 | 18:23 | 13:01 | 2b |
| Fyer et al. [89], 1987 | 8:05 | 5:00 | 1a |
| Griez et al. [90], 1987 | 12:11 | 9:01 | 1a |

PD panic refers to the number of participants in each study with panic disorder that exhibited panic attack symptoms; control panic refers to the number of participants in control conditions that exhibited panic attack symptoms.

*$CO_2$-35% Inhalation*

Similar results were obtained for $CO_2$-35% inhalation. Of 16 identified studies, 10 were step 1a, and 6 studies qualified for steps 2a or 2b (Table 3). A logistic regression was conducted to predict panic attacks as a binary outcome following $CO_2$-35% inhalation, with PD status used as s a predictor variable. A test of the full model against a constant-only model was statistically significant, revealing that panic attacks following $CO_2$-35% inhalation can reliably distinguish between individuals with and without PD ($\chi^2$ = 161.86, $p < 0.001$, $\varphi = 0.498$, df = 1). A Nagelkerke's $R^2$ value of 0.327 indicates a moderately strong relationship between PD status and panic attacks, with a prediction success of 73% (86.4% for PD and 66% for control). An observed Wald statistic of 119.91 demonstrated that PD status made a significant contribution to prediction ($p < 0.001$), with an Exp (*B*) value of 12.24, revealing that individuals with PD are 12.34 times more likely to have a panic attack following $CO_2$-35% inhalation than individuals without PD.

These results indicate that $CO_2$-35% demonstrates potential as a diagnostic laboratory test, as individuals with PD are more likely to respond to $CO_2$-35% than individuals without PD. Based on this relatively small body of literature, 6 studies were identified as step 2a or 2b (i.e., including a related patient control group). Caldirola et al. [33] found that $CO_2$-35% inhalation was similarly panicogenic in groups of PD and social phobia patients. On the other hand, Perna et al. [34] found $CO_2$-35% inhalation significantly induced more panic symptoms in PD patients as compared to MDD patients with no history of panic attacks. Even more significant, in terms of clinical utility, were the reported differences in responses between individuals with both PD and obsessive compulsive-disorder, individuals with PD alone, individuals with obsessive compulsive-disorder alone, and healthy controls, where the groups with PD reacted to $CO_2$-35%, and individuals without PD did not [35]. The latter 2 studies support the potential clinical utility of $CO_2$-35% inhalation in the differential diagnostic process among psychiatric disorders that need to be differentiated. Relatively more recently, Schutters et al. [36] provided evidence of a differential response to $CO_2$ inhalation between patients with PD and patients with

social anxiety disorder further supporting the potential usefulness of $CO_2$ inhalation in differentiating among the various anxiety disorders.

Taken together, the results of our analyses indicate that both sodium lactate infusion and $CO_2$-35% inhalation can induce panic attacks in individuals with PD, and that this effect is greater for individuals with PD than comparison groups. Additionally, our results highlight that the vast majority of existing literature is categorized as step 1a, and that there is a need for step 1b, 2a and 2b research.

## Discussion

### *Review of Findings*

The present study was designed to investigate the status of development for sodium lactate infusion and $CO_2$-35% inhalation as diagnostic measures of PD. To date, the field has relied on behavioral and self-report measures to diagnose psychiatric illness and has lagged behind traditional medicine in validating and implementing laboratory measures as diagnostic tools [4]. This is a limiting step in the field, as developing laboratory tests for pathology may support PD diagnosis particularly in settings where psychiatrists or psychologists are unavailable, when diagnosis is uncertain, as well as advance our understanding of the mechanisms that perpetuate and differentiate psychiatric illnesses. Even though the field has identified physiological responses suggestive or characteristic of internalizing and externalizing disorders [2, 3, 37], psychiatric medicine has largely been unable to establish clinical norms or standardized procedures for using these laboratory measures to diagnose [10]. Thus, there has been a push in recent years to standardize how the viability of these laboratory measures can be determined.

In an attempt to bridge this limitation in the field, we conducted a literature review and identified relevant studies that compared panic-like symptoms in individuals with PD and comparison groups following the administration of either sodium lactate or $CO_2$-35%. Additionally, we used the 3-step approach proposed by Arfken et al. [1] to categorizing each study to help assess the state of development and potentially usefulness of these ancillary measures.

Our findings revealed that both sodium lactate infusion and $CO_2$-35% are significantly more likely to induce panic attacks in individuals with PD than controls, and that this effect was greater for sodium lactate than $CO_2$-35%. By using the 3-step approach, we also identified that the majority of studies examined in this review were step 1a. Taken together, these findings suggest that both sodium lactate and $CO_2$-35% could be helpful diagnostic tools for PD, but that they are underdeveloped, as very few studies have sought to establish clinical norms or compare PD to other related disorders.

This literature review and series of analyses did not identify any studies using sodium lactate infusion as step 1b studies, and only 2 of 22 studies as steps 2a or 2b. Additionally, no studies using $CO_2$-35% inhalation were identified as step 1b, and only 6 of 16 studies were identified as steps 2a or 2b. Collectively, this suggests that the field needs to place greater emphasis on steps 1b, 2a, and 2b to determine the role that sodium lactate infusion and $CO_2$-35% inhalation may have in diagnosing PD. More specifically, future step 1b studies should assess sensitivity to sodium lactate infusion and $CO_2$-35% inhalation for individuals with PD to help establish cutoffs based on panic presentation. Once the field is able to do this, the next steps would be to assess how well these 2 panicogens can discriminate between PD and related pathologies (step 2a), and develop cut points and measures of sensitivity to differentiate PD from other pathologies and better understand heterogeneity within the PD diagnosis (step 2b).

### *Limitations, Implications for the Field, and Future Directions*

Despite the promise that both sodium lactate and $CO_2$-35% show as diagnostic tools for PD, the present study is not without limitations. To this end, different criteria for panic attacks were used across the studies included in the present set of analyses. Niccolai et al. [38] defined panic attacks as an increase in 25 units or more on a visual analogue scale for anxiety and the presence of 4 symptoms from the panic symptom list. These criteria for a panic attack are in contrast with those of Perna et al. [39], who relied on guidelines from earlier research [40], defining panic attacks as the presence of fear or panic, along with 4 symptoms from the DSM-III-R, including at least 1 cognitive symptom (e.g., fear of dying or going crazy).

Despite this limitation, it should be noted that the present review is not aimed at creating a standardized approach for diagnosing panic disorder with sodium lactate infusion or $CO_2$-35% inhalation, but rather it was designed to help identify the current state of the field using a previously used 3-step approach to identify current limitations of the field. In line with the 3-step approach, future researchers should be more specific and consistent with their cut points (step 1b) and help produce a stan-

dardized procedure (step 3) to ensure that the onset of panic following administration is consistent and not contingent upon varying criteria [1].

Furthermore, a number of studies in the present review relied on self-reported panic symptoms following the administration of sodium lactate or $CO_2$-35%. If the field truly seeks to use objective measures of pathology, then future researchers examining the utility of these panicogens should consider using physiological indices, such as the startle eyeblink and the P300 event-related potential component. A 2012 study compared $CO_2$-35% inhalation to a placebo condition in a group of healthy controls and demonstrated that $CO_2$-35% inhalation was associated with attenuated startle eyeblink [41]. Similarly, Alius et al. [42] were able to replicate this finding of attenuated startle eyeblink during an interrupted breathing task and also demonstrated that the P300 amplitude is smaller during periods of interruption, suggesting that the presence of $CO_2$ may have an effect on physiological indices of emotion and awareness. Future research using the 3-step approach to determine the usefulness of sodium lactate and $CO_2$-35% should consider using physiological indices, as these indices have received increasing attention in pathology research and show promise as useful outcome variables [43].

First and foremost, both sodium lactate and $CO_2$-35% may be viable tools for diagnosing PD, but additional research is needed to determine if these reactions are unique to PD, and if there are subsets of individuals with PD who do not respond to these agents. Notably, researchers have voiced concerns about the historic overreliance on self-report and behavioral measures in diagnosis, as current standards determined by the DSM-5 and International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) [44] cannot account for the heterogeneity of psychiatric diagnoses [45]. Strik et al. [46] have emphasized this concern, noting that our current conceptualization of pathology limits our ability to understand and study the biological mechanisms that perpetuate these diseases, as well as our understanding of heterogeneity in disease presentations. If laboratory measures are able to identify individuals with certain pathologies or differentiate subgroups of individuals in a diagnostic category that respond to certain measures, we may be able to better understand underlying characteristics that result in different presentations within a singular diagnosis.

Providers who treat PD know that the diagnosis presents itself differently across patients, and in recent years, empirical evidence has provided evidence for this heterogeneity [47]. Roberson-Nay and Kendler [48] suggest that 2 PD subtypes may exist, one characterized by *respiratory* symptom sensitivity and another characterized by *general somatic* symptoms. If these 2 subtypes of PD do exist, it may be helpful for future research to examine reactions to panicogens between these two subgroups, specifically conducting a step 2b study by comparing responses between the *respiratory* and *somatic* subtype of PD following $CO_2$-35%.

If it can be determined that panic symptoms following sodium lactate infusion or $CO_2$-35% inhalation are not unique to PD, but rather that individuals across diagnostic categories respond, then there could be shared characteristics across disorders responsible for this reaction. A recent study further highlights this possibility, as the researchers demonstrated that PTSD individuals were more likely to exhibit panic attacks following $CO_2$-35% inhalation compared to a control inhalation condition [49]. This response may be present in individuals with PTSD because of a transdiagnostic characteristic also found in PD. *Anxiety sensitivity*, or the predisposition to interpret symptoms of arousal as dangerous [50], could be a variable found across many disorders that could be responsible for this sensitivity to panicogens. Telch et al. [51] provided evidence for this by exposing college students with self-reported high and low levels of anxiety sensitivity to $CO_2$-35% and showed that individuals high in anxiety sensitivity were more likely to exhibit panic attacks than their low-anxiety sensitivity peers. Coupled with our findings, a logical next step for researchers would be to conduct step 2a studies comparing panic-like reactions following sodium lactate or $CO_2$-35% in individuals with PD, as well as other disorders where elevated anxiety sensitivity is common, such as PTSD, obsessive compulsive disorder, and generalized anxiety disorder [49, 50, 52], respectively.

If sodium lactate infusion and $CO_2$-35% inhalation are determined to be appropriate diagnostic tools, $CO_2$-35% inhalation could be preferred over sodium lactate infusion. Sodium lactate infusion requires an intravenous catheter to be inserted into the arm and can take up to 40 min, while $CO_2$-35% inhalation only requires 1 vital capacity inhalation [53–55]. The noninvasive nature and relatively small period of time required for $CO_2$-35% inhalation are major strengths of this potential diagnostic tool. Other noninvasive laboratory measures that have been examined as diagnostic tools, such as EEG and fMRI, are more time consuming and costly than $CO_2$-35% inhalation, and require extensive patient involvement [56, 57].

The administration of $CO_2$-35% is easy so as it may make it an attractive diagnostic tool for health care settings where psychiatric evaluations are not feasible. Individuals with anxiety disorders, including PD, generally

present to hospitals and primary care settings before seeking specialized treatment [58–61]. It would be a major step forward if future research can expand on current findings that $CO_2$-35% induces panic attacks in individuals with PD by testing whether or not this effect is unique to PD. More specifically, medical professionals who do not specialize in psychiatric diagnosis or care typically see these individuals before psychologists or psychiatrists, and arming them with an easy-to-administer diagnostic tool (i.e. $CO_2$-35%), may aid in referring individuals with PD to appropriate treatment.

## Conclusion

The development of ancillary diagnostic procedures is important to help the field move forward, as accurate psychiatric diagnosis remains the major limiting step in biological research and treatment studies [9]. In the present review, we provide evidence that (1) both sodium lactate and $CO_2$-35% are more likely to induce panic attacks in individuals with PD than controls, and (2) that the clinical utility of these chemical agents remains understudied, as most studies have compared individuals with PD to healthy control participants. In order to expand on the findings of this large body of research, it would be prudent to recommend the field to continue to examining the utility of these agents with step 1b, 2a, and 2b studies.

Since the 1980s, research has identified tests that can induce panic attacks in PD patients. Despite significant accumulated literature, panic induction has not matriculated into a diagnostic test in clinical psychiatric medicine. Battaglia and Perna [62] had enough data so as to provide the field with ROC analysis for $CO_2$-35% inhalation in inducing panic attacks in PD patients, but a similar work was not provided for the sodium lactate infusion despite an equally impressive body of literature. Much research remains needed to accurately delineate the clinical utility of these procedures in differentiating PD from other anxiety disorders. Once the field is able to do so, these tests may be able help us understand the heterogeneity of PD, as well as facilitate appropriate diagnosis and referral.


## Acknowledgments

The authors would like to acknowledge the contribution of Dr. Mashal Khan to the early phase of this effort in identifying relevant literature and Anthony Schmeidler for his effort in organizing the manuscript.


## Statement of Ethics

This work did not include human subjects and did not require ethics committee approval.

## Disclosure Statement

None of the authors has conflicts of interests with the work described in this paper.


## Funding Sources

The work was partially supported by a local grant from the Department of Psychiatry, Friends of Psychiatry Foundation at the University of Missouri-Kansas City, and The Saint Luke's Marion Bloch Neuroscience Institute.


## Author Contributions

Andrew D. Wiese, worked extensively on literature identification, review, data extraction and manuscript development; Nash N. Boutros lead and guided the entire effort.

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