Mind over matter in biological conditions:

The role of psychological processes in lactose intolerance and chronic spontaneous urticaria

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Abstract

Historically, medicine has emphasized biological models of illness, while ignoring their psychological dimensions. This outlook has been emphasized further in the recent era of genetic research. In spite of our best efforts, however, certain conditions that clinicians consider exclusively rooted in biology have remained difficult to manage. In order to demonstrate the importance of psychological factors in such conditions, this thesis examines the role that psychological factors play in lactose intolerance and chronic spontaneous urticaria.

Findings from Study 1 and its corresponding pilot project suggest that expectancies are a key mechanism in lactose intolerance. Specifically, expectancy manipulations led self-reported lactose intolerant individuals to develop common intolerance symptoms (bloating, abdominal pain, and flatulence). Findings from Study 2 reveal that psychosocial factors appear to be implicated in the onset and development of chronic spontaneous urticaria.

These results may lead to the development of new psychological interventions to alleviate lactose intolerance (through expectancy-manipulation) and chronic spontaneous urticaria (through negative thought process de-automatization, as outlined in Commentary Response 1).

Finally, this thesis addresses the ethical dilemmas which may accompany psychologically-targeted treatments, and suggests a method through which deceptive practices may be ethically employed to benefit patients.

Résumé

Bien que la médecine s'intéresse aux modèles biologiques de la maladie depuis bien longtemps, elle a tendance à ignorer les dimensions psychologiques associées à ces modèles. Cette perspective incomplète s'est amplifiée au cours des dernières années avec l'expansion des recherche dans le domaine génétique. Malgré les plus francs efforts des chercheurs et des cliniciens, cependant, certaines maladies considérées comme essentiellement biologiques demeurent difficiles à comprendre et à contrôler. Défendant l'importance des facteurs psychologiques associés à de telles conditions, la présente thèse vise à comprendre le rôle des facteurs psychologiques dans l'intolérance au lactose et l'urticaire spontanée chronique.

Les résultats de l'étude 1 ainsi que du projet pilote associé suggèrent que les attentes jouent un rôle clef dans l'intolérance au lactose. Plus spécifiquement, manipuler les attentes des participants intolérants au lactose suffirait à déclencher des symptômes typiques de cette condition (ballonnements, douleur abdominale et flatulences). Les résultats de l'étude 2, quant-à-eux, révèlent que des facteurs psychosociaux seraient impliqués dans la génération et le développement de l'urticaire spontanée chronique.

Ensemble, ces résultats nous mènent à considérer de nouvelles interventions psychosociales pouvant potentiellement réduire les symptômes de l'intolérance au lactose (en manipulant les attentes) et de l'urticaire spontanée chronique (en désactivant les processus de pensée négative tel qu'illustré dans la Réponse Commentaire 1 [Commentary Response 1]).

Enfin, la présente thèse examine les dilemmes éthiques générés par les traitements visant la manipulation des aspect psychosociaux liés à ces conditions et suggère un moyen d'employer de telles déceptions d'une manière éthique pour le bénéfice des patients.

Statement of Original Contributions

The present thesis consists of three original manuscripts. By exploring lactose intolerance and CSU, we have shown that even conditions with strong genetic roots remain affected by psychological factors. These findings create a solid foundation for further experimental work with both lactose intolerance and CSU, and suggest that psychological interventions may eventually emerge as viable therapies. In accordance with our beliefs that placebos may emerge as a viable option for psychological intervention, we have also explored the ethical dilemma surrounding their use in the clinic. Manuscript 1 is being submitted for peer-review in *Digestive and Liver Diseases*. Pilot Study 1 was presented at the Annual Meeting for the Society of Clinical & Experimental Hypnosis. Manuscript 2 was published in the peer-reviewed journal *Allergy*. Manuscript 3 is being readied for peer-review submission to the *British Medical Journal*.

Contributions of Authors

Three original manuscripts and one commentary response comprise the present thesis. The first manuscript is co-authored by myself, Dr. Cory Harris, and Dr. Amir Raz. Dr. Raz developed the methodology for the subsequent pilot study, Dr. Harris worked with me on the manuscript, while I collected the literature and drafted the manuscript. In addition, I collected and analyzed the data for the pilot study. For the second manuscript, I collaborated with Dr. Ben-Shoshan on the study selection and analysis, as well as drafting and editing. Dr. Raz ensured that the hypnosis-related section of the paper was appropriately written, and guided the process with his impeccable eye for detail. For the commentary response, Natasha Campbell worked on the first set of comments regarding result replication, and I addressed the second set, regarding hypnosis. Michael Lifshitz and Dr. Raz were involved in the editing process. Finally, I drafted and edited the third manuscript, with conceptual suggestions by Dr. Raz.

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General Introduction

The history of medicine is, in essence, one of luck and hubris. From ancient remedies of bloodletting and trepanation, to modern day homeopathy and Reiki, the therapeutic domain is replete with unsound, misguided and dangerous practices (Harrington, 2008). The fact that these panaceas have no evidence to support them, however, has done little to silence their proponents, and scientific exposes of, say, crystal healing practices—to pick but one among the vast number of "alternative medicines"—remain commonplace (Ernst, 2011).

Since antiquity, shamans, priests, and physicians attempted to understand the world to the best of their abilities, and channelled their insights into forms of healing (Hitchens, 2007). While astronomers and physicists made impressive strides in understanding nature's workings through mathematics and careful observation, medicine men struggled to understand the processes which governed the human body. With dissection and autopsy frequently forbidden by authorities, the study of physiology languished; thus, with the corporeal relegated to the domain of conjecture, there was little else but unfalsifiable assumptions to use as basis for devising treatments (Pleszewski, 2007). Nevertheless, these therapies seemed to have worked. We remained, therefore, confident in a number of these assumptions (e.g., Aristotle's belief that the body required us to manually balance its four humours—yellow bile, black bile, blood, and phlegm—in order to remain healthy) for long periods of our history. This self-assuredness led to misguided cures, but was very much necessary; if anything, this confidence in our medical understanding only bolstered the placebo effects on which the majority of these therapies were predicated (Hunt, 2007).

In spite of its late start, medicine made impressive strides in recent centuries. Germ theory has led medicine out of the cave, and the spread of medical research has resulted in

antibiotics, vaccines, and vast numbers of beneficial therapies (Hitchens, 2007). That many of the most useful medical discoveries have come about through sheer luck (e.g., electroconvulsive shock therapy, the use of lithium in schizophrenia) is, perhaps, irrelevant: medicine seemed to be on the right track (Hunt, 2007). In no small part due to Karl Popper's emphasis on falsifiability—the philosopher believed that the hallmark of rigorous science was theories being formulated in a way that allowed them to be proven right or wrong (Popper, 1962)— we gradually transitioned away from an emphasis on Platonic deduction to Aristotelian induction; the observable explanations provided by biology attained medical supremacy.

Meanwhile, the study of the mind flourished—largely owing to Freud's radical theories. Unfortunately for psychology, however, it came to be associated with the unfalsifiable postulates and fantastical claims characteristic of psychoanalysis; to the wider medical community, the whole endeavour was less science and more fiction (Hunt, 2007). Although the discipline has made tremendous efforts to foster academic rigour (perhaps in an attempt to compensate for its first theories), a large part of the medical community seems convinced that psychology was a lesser science. As a result of these doubts, psychology and medicine have yet to embrace each other.

The dearth of consideration that medicine affords psychology has led to two regrettable outcomes. The first is that a sizeable portion of medical research remains firmly attached to the mechanistic view of the human body (Harrington, 2008). This conception, wherein one bodily system is overtly linked to others through biologically accessible processes, can lead to superficial theories that overlook the complexities arising from psychological factors. The direct corollary of such rigid biological models leads to the development therapies and best-practice guidelines which fail to address important psychological concerns. The second consequence is

the result of this disciplinary isolation: a widening gap between research and practice, leading to sub-optimal patient care (Borys, 2008).

With recent advances in biology, genetic explanations for medical conditions have grown in popularity. While genetics provides medicine with a novel outlook, the scope of research shifts closer to biology, and further from psychological factors. Certain conditions, however, remain difficult to treat, in spite of what appear as relatively straightforward biological antecedents. Such conditions may incorporate important psychological parameters, and would benefit from careful examination with specific attention afforded to mind-body interactions.

Lactose intolerance and Chronic Spontaneous Urticaria (CSU) are especially well suited to such explorations. Genetic research over the past decade has identified the basis for intolerance (N.S. Enattah et al., 2002); that tolerance to lactose is a relatively recent development in human history (Itan, Powell, Beaumont, Burger, & Thomas, 2009); and that cattle milk protein genes and human genes responsible for the enzyme which digests lactose evolved simultaneously (Beja-Pereira et al., 2003). In spite of this, lactose intolerance remains difficult to both diagnose and manage.

CSU, an idiopathic form of hives, likewise poses a problem for clinicians. The condition, which consists of transient, itchy wheels, has no known trigger, and may severely impact an individual's quality of life (Ozkan et al., 2007). Moreover, only 50% of sufferers are symptom-free after five years. In Canada, CSU falls under the domain of allergists; problematically, however, allergy medications are frequently ineffective, and leave patients with little recourse (Buffet, 2003). Finally, in spite of over eight decades' worth of research, we have been unable to elucidate its biological trigger (Stokes, Kulchar, & Pillsbury, 1935).

Thesis Rationale and Objectives

In order to bridge the gap between psychology and biology hampering medicine, this thesis examines the role that psychological factors play in conditions that the clinical community considers solely rooted in biology. First, it will address inconsistencies within the lactose intolerance literature: although we understand the physiological processes involved, the condition remains difficult to both manage and diagnose. Secondly, the thesis will address the role of psychological factors in CSU. While we have a reasonable outline of the biological processes underpinning this condition, we have been unable to provide a consistently and effectively to alleviate its symptoms. Although other conditions with psychological determinants exist (e.g., asthma, which other students in my laboratory have been researching, has important psychosocial determinants (Wright, Rodriguez, & Cohen, 1998)), lactose intolerance and CSU appeared as ideal choices in light of my presently available resources, such as the participants for the pilot study, the accessibility of full-text studies, as well as my research interests. Finally, in addition to exploring the psychological factors involved in these conditions, this thesis will also discuss the ethical dilemma which arises from using placebos as a potential treatment mechanism.

Review article: Psychological mechanisms in lactose intolerance -

Bridging the gap between lactose consumption and symptom development

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Abstract

Background: Lactose intolerance (LI) is widespread among adults and can influence dietary behaviours, nutritional status, health, and quality of life. Despite our basic understanding of its contributing parameters, a gap persists between LI diagnostic status, lactose consumption and symptom development. **Aim:** In this paper, we review recent clinical literature to examine the disparity between both diagnosed intolerance and lactase non-persistence, and the occurrence of symptoms in patients following lactose consumption. **Methods:** We conducted a search of the PubMed and Web of Science databases using combinations of the keywords "lactose intolerance", "lactose", "lactose maldigestion," "psychology", "expectancies", including full-text accessible articles in English. We then reviewed the references of all collected sources to identify additional literature of interest. **Results:** While many individuals diagnosed with lactose intolerance remain asymptomatic after consuming considerable amounts of lactose, people who retain the capacity to digest lactose frequently experience symptoms after consuming a negligible quantity of dairy. Moreover, individuals who believe they are intolerant – regardless of diagnostic status – frequently report symptoms, even following a lactose-free challenge. **Conclusion:** Applying a psychological framework to bridge the gap between lactose consumption and symptom development, we propose that expectancies underlie much of the variation in individual responses to dairy, and that a greater appreciation for psychological contributions to LI by both practitioners and patients will improve diet and symptom management.

Introduction

By several estimates, lactose intolerance (LI) affects the majority of the world´s population (Andersson, Dotevall, Dahlqvist, & Walan, 1970; Itan, Jones, Ingram, Swallow, & Thomas, 2010). In spite of this widespread prevalence, common notions of LI among both practitioners and the public tend to be simplistic.

Many people lose their natural ability to metabolize lactose as they age, with this decline in metabolic capacity resulting in gastrointestinal symptoms after eating too much dairy. Clinical research, however, consistently shows a marked gap between lactose intake and subsequent symptom formation, regardless of LI diagnostic status. Lactase deficient individuals do not always experience symptoms after consuming lactose, while those with adequate lactase activity are not always symptom-free (Vesa, Korpela, & Sahi, 1996). Apparently, lactase activity is not the only factor contributing to LI. Evidence from diverse experimental and clinical paradigms suggests that individual biology is but one determinant of physiological responses to lactose intake (Shaukat et al., 2010).

In the present paper we examine the relationship between diagnostic status, lactose ingestion and symptom development in clinical LI research. After outlining some of the difficulties involved in diagnosing LI, we review a number of studies that highlight notable inconsistencies between diagnosis and symptom formation. Building on recent advances in the study and treatment of pain and irritable bowel syndrome (IBS), we propose psychological factors, most notably expectancies, as the missing link underlying the documented variations in LI symptom presentation.

Expectancies relating to dairy contribute not only to an individual's lactose responses, both in the clinic and at home, but to their future food choices and dietary behaviours as well.

While practitioners (doctors, dieticians and others) acknowledge a role for patient psychology in LI, many consider this role limited to people who continue to report problem with dairy despite a negative diagnosis. However, as we demonstrate below, psychology influences the responses of the severely intolerant as well. With greater appreciation for psychological influences in LI, practitioners will be better equipped to diagnose the condition and discuss management strategies with patients. Moreover, as a modifiable determinant of symptom development, expectancies offer a viable tool for managing symptoms and improving quality of life.

A brief primer

The lactase enzyme cleaves lactose present in mammalian milk into monosaccharides for uptake from the intestinal lumen into the bloodstream. This enzyme is abundant in newborns and, decreasing with age, persists into adulthood to varying degrees (Harrington & Mayberry, 2008). Many individuals, however, do not produce adequate amounts of lactase to break down the lactose they consume. Known as lactase non-persistence (LNP, also referred to as hypolactasia), this condition results in lactose maldigestion, where colonic microflora ferment the undigested lactose, leading to the production of hydrogen and other metabolic by-products. These by-products, together with increased osmotic pressure and water retention, contribute gastrointestinal symptoms such as abdominal pain, bloating, stomach rumbling, or flatulence. When maldigestion is paired with symptoms following a lactose challenge, a diagnosis of LI is deemed appropriate (Gasbarrini et al., 2009).

Research into the rates of LNP documents a wide variation in global and ethnic prevalence. Whereas in the United States the prevalence is 15% among Caucasians, 53% among Mexican-Americans, and 80% in Blacks, proportions reach almost 100% in certain Asian countries (Sahi, 1994; Scrimshaw & Murray, 1988). It is crucial to remember, however, that

prevalence estimates are for LNP, not LI. Research in Sicily, for example, demonstrates that, among a random sample from the general population (n=323), 32% were LNP but tolerant, whereas only 4% were LNP and intolerant (Carroccio, Montalto, Cavera, & Notarbatolo, 1998). Regardless of prevalence, the diagnosis of LI is only as accurate as the supporting clinical tests practitioners typically employ.

Supporting Diagnostic Tests

Clinicians frequently assess LNP using the hydrogen breath test (HBT), wherein they measure the amount of hydrogen in expired air following the consumption of a standardized lactose challenge. Other assays, such as blood glucose (also known as the lactose tolerance test, or LTT), stool acidity, or internal biopsy analyses are more invasive, and are therefore less common (Hermans, Brummer, Ruijgers, & Stockbrugger, 1997; Scrimshaw & Murray, 1988; Vesa, Marteau, & Korpela, 2000). The most recent method involves genetic testing for single nucleotide polymorphisms (e.g. C/T-13910) correlated with a deficiency in the lactase enzyme (N. S. Enattah et al., 2002), While genetic and phenotypic (HBT and LTT) test results are highly correlated, with all offering similar diagnostic value in terms of hypolactasia, they do not provide a reliable link to symptoms and, therefore, LI (Di Stefano et al., 2009; Marton, Xue, & Szilagyi, 2012).

Many physicians are aware of the lack of direct relationship between LNP-based maldigestion and symptoms, and may diagnose LI based solely on patient interviews and self-reported symptoms. These methods are not wholly reliable due to their singular dependence on one-off subjective accounts, and the likelihood of falsely attributing symptoms to lactose consumption (Di Stefano et al., 2009; Suarez, Savaiano, Arbisi, & Levitt, 1997). Whether lactase persistent or non-persistent, people who perceive themselves as LI tend to retroactively

exaggerate the severity of domestic symptoms relative to those reported in a clinical setting (Suarez et al., 1997). Moreover, research on memory confirms that personal accounts are susceptible to leading questions, which arise naturally in the clinic as practitioners search for diagnostic clues (Vesa et al., 1996). When a patient presents with recurrent gastrointestinal symptoms – a common occurrence – practitioners invariably inquire about dairy consumption. As a secondary tool, clinicians may recommend avoiding dairy and monitoring whether or not symptoms abate. This practice, however, can easily lead to false attribution and may contribute to the high number of individuals who self-report as LI but are actually lactase persistent (Carroccio et al., 1998; Johnson, Semenya, Buchowski, Enwonwu, & Scrimshaw, 1993; Suarez, Savaiano, & Levitt, 1995).

In sum, the battery of tests used to diagnose LNP lack of both validity and reliability as independent diagnostic tools for LI. The various markers of maldigestion consistently fail to correlate with the occurrence of physiological symptoms, and self-reported symptoms suffer from the vagaries of memory and misattribution. As a result, a wide gap emerges between the assessment of LI and the manifestation of its symptoms, forcing clinicians to rely on insufficient or unreliable information, and leaving patients vulnerable to false expectations.

A gap in the evidence

A persistent disparity between lactose maldigestion and symptoms has long marked the LI literature. Indeed, studies frequently note that individuals who claim intolerance can consume moderate amounts of lactose, despite being maldigesters. Alternatively, individuals with both deficient and persistent lactase activity often develop symptoms after consuming lactose-free foods.

Absence symptoms in response to lactose

Whereas high doses of lactose (>50g) taken on an empty stomach cause symptoms in the majority maldigesters, responses to low doses of lactose are generally unaffected by individual lactase levels (Beyerlein et al., 2008; Casellas, Varela, Aparici, Casaus, & Rodriguez, 2009). Double-blind trials with people reporting severe LI demonstrate that most individuals can, in fact, tolerate one cup of milk (approximately 12g of lactose) with negligible symptoms (Suarez et al., 1995). Follow-up research reveals that they could consume two cups of milk, one at breakfast, and one at dinner, with only minor symptoms proportional to those experienced by lactase persistent participants in the control group. In fact, self-described intolerants rated symptoms (e.g., abdominal pain, bloating, stomach rumbling) after consumption as trivial (Suarez et al., 1997). A systematic review investigating the maximum dose of lactose tolerable to individuals with LI or maldigestion found similar results: most could tolerate 12-15g, and insufficient data were available to confirm the hypothesis that solutions with 0-2g of lactose led to less severe symptoms than those with 12g (Shaukat et al., 2010). Such findings suggest that low doses of lactose, as well as larger doses coupled with meals or staggered in time, are sufficiently metabolized by self-proclaimed intolerant individuals to avoid symptoms.

Symptoms in response to lactose

Another course of research, comprising of a randomized double-blind crossover study of previously diagnosed lactose maldigesters and digesters, showed no differences in symptoms between participants who consumed 7g of lactose and those who consumed none (Vesa et al., 1996): all participants, in both diagnostic groups, demonstrated symptoms of lactose intolerance suggesting a lack of physiological differentiation between these amounts. These results suggest that even when symptoms do occur at low doses (0-7g), lactase activity does not contribute to their formation. Research by Suarez at al. points to an additional contributing factor (Suarez et

al., 1995): while gastrointestinal symptoms following milk consumption were minimal for participants regardless of their status as maldigesters or digesters, during the selection of maldigesters for the study, 30% of the participants were identified as lactose digesters who manifested symptoms with no known physiological cause. Observations of maldigesters and digesters developing symptoms to quantities of lactose that previous studies have deemed negligible, as well as findings of digesters manifesting symptoms with no physiological reason, suggest that lactose and lactase are not the only contributors to LI symptoms (Shaukat et al., 2010; Suarez et al., 1995).

Such inconsistencies between physiological lactase activity and symptom manifestation also emerge from research examining lactose maldigestion among African Americans. Recruiting participants who claimed to experience symptoms after consuming milk, one study measured the extent to which reported symptoms corresponded to lactose intake (Johnson et al., 1993). After selecting a group of lactose maldigesters using the HBT, the experimenters offered participants lactose-containing or lactose-free milk in repeated trials. One third of all maldigesters manifested symptoms to both solutions, suggesting that lactose was not responsible for a third of these effects. Moreover, the study's selection procedure revealed 15% of the participants to be lactose digesters who nonetheless exhibited symptoms with no clear physiological cause. Once again, these results indicate that a parameter *other* than lactose metabolism underlies the manifestation of LI symptoms, at least in some people and situations.

Meta-analytic findings lend the strongest support to this conclusion (Savaiano, Boushey, & McCabe, 2006). Researchers examined 21 studies contrasting maldigesters' responses to placebo or to quantities of lactose typically found in meals (up to 12g), and found that lactose itself was not a major cause of symptoms. Moreover, when researchers assessed 353 patients

referred for an HBT, they found that participants would retrospectively rate their reaction to lactose consumption at home as much more severe than their reaction to their consumption of lactose in the laboratory, as part of the HBT (Casellas, Aparici, Casaus, Rodríguez, & Malagelada, 2010). Curiously, patients' home meals were likely to contain much less lactose (only 25%) than the 50g used in the HBT. Numerous teams have suggested that psychology, in addition to biology, may contribute to such disparate results (Shaukat et al., 2010; Suarez et al., 1997)

The role of psychology

LI research has tended to refrain from examining the role of mental factors in symptom development, particularly at the experimental level. Nevertheless, psychological mechanisms contribute meaningfully to self-perceptions and clinical diagnoses of LI.

Certain personality traits may predispose individuals to experience subjective bodily complaints with no visible organic cause. In a recent study of 109 individuals referred to a gastroenterology unit, researchers found a greater proportion of LI (29%) than maldigestion (18%) in the sample, in response to a low-dose (15g) HBT (Tomba, Baldassarri, Coletta, Cesana, & Basilisco, 2012). LI and maldigestion were not associated, and symptoms were less severe in patients with maldigestion. Although results suggested that patients' tendencies towards the mental trait of somatization—the reporting of subjective somatic complaints with no evident organic causes—were associated with LI symptoms, previous research found no pathological somatization scores in severe LI sufferers (Suarez et al., 1997).

Additionally, classical conditioning may lead to robust gastrointestinal symptoms in individuals who previously experienced unrelated symptoms after eating dairy (Bernstein, 1999). Alternatively, at the conscious level, misattribution can mislead people to retrospectively ascribe

unrelated gastrointestinal symptoms to dairy (Schacter, 1999). Consistent diagnostic anomalies comprising of lactose absorbers who develop symptoms and maldigesters who do not, however, may also result from a broader and more pervasive mechanism, fed by both conditioning and misattribution: expectancies.

Expectancies

Rotter, first to systematically theorize on expectancies, defined them as the beliefs that certain stimuli predict other stimuli (1954). Rotter postulated that the likelihood of performing a behaviour depends, in part, on the value of its reinforcer, and the expectancy that the behaviour will bring about the desired outcome. While Rotter applied this strictly to voluntary behaviour, such as exercising to reap the benefits of good health, Kirsch expanded the concept of expectancies to include involuntary responses (1985, 1997a). Specifically, Kirsch hypothesized that non-voluntary reactions such as emotions, sexual arousal, or pain, also have reinforcement value, and that one's expectancies relating to their occurrence as a result of particular behaviour strongly affect whether or not that behaviour will be performed.

Positive response expectancies may lead to numerous psychological changes ranging from sexual arousal, increased alertness and drowsiness to relief from anxiety and other conditions (Ross & Buckalew, 1983). These states are not simply subjective, however – they can lead to objective physiological responses, including variations in blood pressure, heart rate, and gastric function (Ross & Buckalew, 1983). Although such changes are difficult to explain at the molecular level, researchers posit that physiological changes stem from mental changes, since psychological states naturally have corresponding physical states (Kirsch, 1985).

Negative expectancies can likewise lead to adverse effects (Hahn, 1997). A study with students expecting to experience headaches in response to the administration of an electrical

current offers strong support. Although the experimenters never engaged the current, 70% of students reported headaches in response to the sham procedure. Remarkably, these headaches persisted even after the students learned that the current was never applied (Schweiger & Parducci, 1981). In addition to internal sources of pain, negative expectancies can also affect exterior physiology; 11 of 13 participants sensitive to a particular noxious plant showed no noticeable skin reaction when exposed to the plant while believing it was harmless (Ikemi, 1962). Conversely, 12 of the same 13 participants exhibited signs of dermatitis when exposed to an innocuous plant believed to be poisonous.

Chronic conditions, such as food allergies, may also be subject to the effects of expectancies, as demonstrated in a double-blinded study of individuals receiving injections of either allergen or saline (Jewett, Fein, & Greenberg, 1990). Both groups manifested the typical allergic reactions (e.g., eye irritation, nausea), in comparable proportions. The most notable finding, however, came when participants received neutralizing injections to alleviate their allergic reactions. The active anti-allergen was no more effective at neutralizing the symptoms than the placebo control – the same saline injection used in the previous condition. In addition to eliciting allergic reactions, negative expectancies can trigger symptoms of asthma, refraction epilepsy, anticipatory nausea, as well as side effects listed on a consent form (Hahn, 1999).

Expectancies in Pain & Irritable Bowel Syndrome (IBS)

The importance of expectancies in pain is well documented. As demonstrated in a formative study by Baker and Kirsch, expectancies of pain sensation directly influence perceptions of pain. When asked to rate the perceived pain of a task that involved immersing their hands in cold water, participants who learned a cognitive coping strategy to temper expectancies reported lower pain scores than participants who did not learn to cope (Baker &

Kirsch, 1991). Numerous groups have confirmed this conclusion using both similar and discrepant experimental paradigms, firmly establishing a role for expectancies in pain (Price, Hirsh, & Robinson, 2008; Sullivan, Rodgers, & Kirsch, 2001; Vervoort, Goubert, Eccleston, Bijttebier, & Crombez, 2006).

Research on IBS – a chronic intestinal condition characterized by abdominal pain, diarrhea, or constipation – suggests that expectancies also contribute to gastrointestinal symptom formation and relief. Meta-analyses of placebo-controlled trials for IBS reveal strong response rates among patients treated with inert substances, suggesting that the condition is responsive to placebo effects and other psychological or contextual cues (Ford & Moayyedi, 2010; Patel et al., 2005). While placebo effects seem to operate through multiple mechanisms, expectancies are an essential component (Stewart-Williams & Podd, 2004). In a study demonstrating the nuanced impact of positive expectancies on symptom relief in IBS, patients were randomly assigned to one of three conditions: waitlist, sham acupuncture, or sham acupuncture coupled with a positive doctor-patient relationship. Despite the absence of any physiologically-based intervention, the proportion of patients reporting adequate relief was 28%, 44%, and 62%, respectively (Kaptchuk et al., 2008).

A recent randomized controlled trial for IBS treatment using open-label placebos offers additional support for expectancies as a determinant of symptom relief. To create positive expectancies in a non-deceptive manner, the researchers told participants that "placebo pills made of an inert substance, like sugar pills… have been shown in clinical studies to produce significant improvement in IBS symptoms through mind-body self-healing processes," prior to randomization (Kaptchuk et al., 2010). Compared to patients in the no treatment arm, placebo-

treated individuals reported lower symptom severity and higher scores for global improvement and adequate relief.

In light of the high comorbidity between IBS and LI, in addition to their shared symptoms and considerable clinical overlap (Vernia, Marinaro, Argnani, Di Camillo, & Caprilli, 2004; Vesa, Seppo, Marteau, Sahi, & Korpela, 1998), we posit that expectancies similarly mediate symptoms of LI.

Expectancies in Lactose Intolerance

A recent study provides intriguing insight into the potential impact of expectancies on symptoms of LI. Experimenters examined 27 participants who had previously exhibited false negatives on the HBT (i.e., showed no increased hydrogen production, but manifested symptoms in response to the 50g of lactose they consumed) (Vernia, Di Camillo, Foglietta, Avallone, & De Carolis, 2010). These participants underwent a sham HBT, receiving 1g of lactose instead of the standard dose (any reaction, therefore, would stem purely from psychological sources), in response to which 12 exhibited symptoms. Of the 54 controls with documented LI, however, 14 also manifested symptoms. Since these findings emerged as part of a larger course of research lacking a randomised control design, we cannot ascertain that these effects arose from expectancies rather than from conditioned responses. Nevertheless, this study demonstrates the notable degree of psychological influence on symptoms.

In addition, the expectancy framework may clarify previously puzzling study results, such as lactose digesters developing symptoms during an HBT, and both maldigesters and digesters developing symptoms to solutions with negligible amounts of lactose (Johnson et al., 1993; Suarez et al., 1995; Vesa et al., 1996). Individuals strongly believing themselves to be intolerant may have robust expectancies of experiencing symptoms during LI assessment—after

all, patients see this as a litmus test identifying those with LI. If their symptoms should ever manifest, patients should expect them to do so at this juncture.

Conclusion

Despite the dearth of rigorous experimental research assessing the role of psychological factors in responses to lactose, expectancies appear to bridge the gap between a diagnosis of LNP – or even LI – and symptoms resulting from lactose ingestion. In addition to elucidating self-reported maldigesters' capacities to tolerate low doses of lactose, and lactase-persistent individuals' manifestation of symptoms, factors such as expectancies, as well as conditioning and personality traits, may help obviate existing confusion about lactose intolerance testing. Physicians frequently attribute non-specific self-reported gastrointestinal symptoms to lactose intolerance, thereby inadvertently imparting similar beliefs on their patients, irrespective of their actual condition. Indeed, research has demonstrated that physicians' attitudes and verbal cues can engender negative expectancies and patients' subsequent clinical deterioration (Benedetti, Lanotte, Lopiano, & Colloca, 2007). The laboratory environment wherein doctors conduct diagnostic assessments of lactose intolerance may further reinforce this belief. Self-professed LI individuals' subsequent abstinence from lactose, coupled with expectations of symptoms following lactose consumption, may condition them to react negatively to the ingestion of any product which they believe contains lactose, further cementing their convictions of LI.

In addition to the negative feedback they provide, such negative expectancies not only impact one's quality of life but also pose a concrete health risk. Despite numerous studies documenting that the majority of LI individuals may consume a moderate amount of lactose and remain asymptomatic (Suarez et al., 1997), many choose to exclude all dairy products from their diets upon diagnosis irrespective of their actual lactose content . In North America, where dairy

is the primary source of calcium but also an important source of other vitamins and minerals, this type of diet may prove dangerous (Fleming & Heimbach, 1994; Matlik et al., 2007). If such individuals fail to consume alternative sources of calcium, their needless excision of dairy will contribute to the development of osteoporosis (Buchowski, Semenya, & Johnson, 2002). And accurate diagnosis of LI is essential to prevent the pernicious development of conditions such as osteoporosis.

In order to control for both patient expectancies and physicians' cues, the ideal diagnosis would involve repeated, double-blind administration of the HBT. Unfortunately, such diagnoses are costly and time-consuming for practitioners and patients alike. Physician and patient education on the potential effects of expectancies (as well as other factors involved in LI) are, therefore, paramount to improving symptom management and dietary planning.

Of course, psychological factors do not wholly explain the discrepancies evident in LI research, with personal eating habits, intestinal microflora, and digestion time contributing to variation in symptoms as well (Szilagyi et al., 2005; Vesa et al., 2000). Nevertheless, LI research frequently mentions, albeit in passing, that psychological factors play a role in symptom manifestation, and our review suggests that they constitute a plausible contributor to LI (Shaukat et al., 2010; Suarez et al., 1995; Vernia et al., 2010). We are, however, are faced with a need for reliable experimental data on the role of expectancies in LI. Only through innovative, interdisciplinary research can we untangle the influence of psychology from that of physiology, and optimize the wellbeing of individuals affected by LI.

Connecting Text: Paper 1 to Pilot Study

Our review of the lactose intolerance literature suggests that expectancies may play an important role in lactose intolerance. While this manuscript provides support for the involvement of psychological processes in symptom development, we require experimental support for such conclusions; otherwise, it is impossible to establish a causal relationship between the development of lactose intolerance symptoms and expectancies.

To ascertain the accuracy of our previous findings, we have devised a short pilot study aimed at assessing the effects of expectancy manipulation on lactose intolerant participants.

The role of expectancies in lactose intolerance symptomatology

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Key Words:

Urticaria, psychology, behaviour, psychosocial factors, mind-body interaction

Methods

The pilot study included 34 volunteers who self-reported as lactose intolerant (11 male; 33 female), aged 18 – 60 years ($M = 27$). We recruited participants through the McGill University Undergraduate Psychology Participant Pool, Craigslist postings, and word-of-mouth advertising by Jewish General Hospital gastroenterologists. The participants did not receive incentives for taking part in the study, however those recruited through the Participant Pool gained course credit. The Jewish General Hospital Research Ethics Office reviewed the ethics protocol (#09-126) and approved the study.

Design

The study employed a 2 x 3 repeated measures design, with expectancy of adverse reaction to lactose (no expectancy of reaction, expectancy of reaction) as the first independent variable, and severity of lactose intolerance (low, medium, high) as the second. The dependent variable was the change in symptoms.

Materials

The pill participants ingested was a standard placebo manufactured by Odan Labs, containing 100mg of lactose—a concentration much lower than the amount the body may detect (Montalto et al., 2008). Participants received a cup of water to drink with the pill, and completed an online survey (see Appendix) on a PC laptop, which included a number of demographic questions, ratings of nine baseline LI symptoms on Likert scales, and a request to watch a short video. The symptoms included abdominal pain, bloating, flatulence, diarrhoea, nausea, headache, loss of concentration, unusual sensation in joints, and sore throat. Participants then answered questions about their first experiences with intolerance, and their assessment of the severity of

their condition. Following this, they rated their symptoms once more. Blood pressure was taken at three points throughout the study using a sphygmomanometer and a stethoscope.

Procedure

The Jewish General Hospital Research Ethics Committee approved this course of research. When participants met the experimenter, they learned that they may ingest lactose throughoutthe study. Once the experimenter gave them a consent form, participants learned that, in their particular case, they would be asked to ingest a substance called β-D-galactopyranosyl-(1→4)-α-D-glucopyranose (a chemical name for lactose). This manipulation created the expectancy that they would not consume lactose. Participants then signed the consent form, and ingested the pill. After participants completed the demographic and baseline symptom questionnaires, the experimenter took their blood pressure. The experimenter then notified them that the substance they ingested was, in fact, lactose, creating the expectancy that they would experience symptoms. Following this, participants watched a video and answered a number of questions, in order to allow for an interval between symptom expectancies and their physical onset. After the completion of the last item and a final blood pressure check, the experimenter debriefed the participants. In total, the study took 30 minutes.

Statistical Analysis

We performed statistical analyses using SAS® v 9.2 (SAS Institute, Cary, NC). The data analysis comprised of descriptive statistics and frequency distributions. We tested hypotheses of interest by performing repeated measures ANOVAs.

Results

We removed responses for 3 participants from the statistical analyses because they misunderstood the pre-expectancy symptom measures, leaving 31 responses. Although blood pressure data were available, they were not part of the analysis.

The effects of Expectancy (Expectancy, No Expectancy) and LI Severity (High, Medium, Low) on Symptom Change were analysed with 2 x 3 repeated measures ANOVAs for each of the 9 symptoms.

A significant main effect of Expectancy emerged, as shown in Table 1. No main effect for LI Severity was found for any of the symptoms, $p>0.05$.

Table 1

Main Effect of Expectancy on Symptoms

Symptom	F (1, 28)	p
Abdominal Pain	4.76	0.0377*
Bloating	10.15	0.0035**
Flatulence	7.04	0.013*
Diarrhoea	0.27	0.6105
Nausea	3.09	0.0895
Headache	0.16	0.6895
Loss of concentration	2.08	0.16
Odd sensation in joints	0	1
Sore throat	0	0.9884

Note. *$p<0.05$

**$p<0.005$

Analyses showed a significant interaction between severity of intolerance and expectancy, with highly intolerant participants scoring significantly higher during post-expectancy measures for bloating ($t(28) <0.005$) and flatulence ($t(28) < 0.05$) than they did for pre-expectancy measures.

Discussion

This pilot study aimed to examine the effects of expectancies on the formation of symptoms in low, moderate, and severe lactose intolerance sufferers. We hypothesized that participants would manifest symptoms upon learning they had ingested lactose, as a result of altered expectancies regarding their physiological responses. We further hypothesized that those with higher self-rated severity of intolerance would experience greater symptoms. The outcomes of the expectancy manipulation supported both hypotheses, suggesting that response expectancies play an important role in lactose intolerance. Specifically, the results imply that expectancies were responsible for the manifestation of abdominal pain, flatulence, and in particular, bloating. We also found that severity of intolerance was an important factor when considering the effects of expectancies, since it was only the highly intolerant participants who showed significant differences in pre/post symptom ratings for flatulence, and especially bloating.

The finding that expectancies affect the formation of LI symptoms is in line with research on the effectiveness of the HBT, which suggests that the negative expectancies may be responsible for symptom formation in a small number of outpatients, but did not specifically address the manner in which this occurs (Vernia et al., 2010). The present pilot study suggests that response expectancies are a mechanism through which symptoms may form, further clarifying results.

The idea that expectancies play a role in LI symptoms also helps to explain several discrepancies in past instances of LI research. In one course of research (Johnson et al., 1993), 33% of African American maldigesters were found to manifest symptoms to milks both with hydrolysed, and non-hydrolysed lactose. This finding may have occurred because even in the

hydrolysed condition, participants expected to experience symptoms. The same study found that 15% of the participants had no difficulty digesting lactose, yet still formed LI symptoms. This penomenon may also be attributable to the role of expectancies, since there was no physiological basis found for their symptoms.

Conclusions drawn from the current study also help explain results of the meta-analysis conducted by Savaiano et al. (2006), which found that moderate amounts of lactose were not the primary cause of symptoms in many severely LI individuals. Since the present study showed that expectancy-based symptoms were greatest for the highly intolerant, we can assume that expectancies played an important role in the studies examined within the meta-analysis. While expectancies may play a role in the development of lactose intolerance symptoms as a whole, the present findings have shown that some symptoms (i.e. abdominal pain, flatulence, and especially bloating) can be elicited more easily than others. There are a number of factors which may be responsible for these results. Firstly, virtually all lactose intolerant individuals experience gut-related symptoms of abdominal pain, bloating, and flatulence, as opposed to a smaller number who experience systemic effects of headaches or unusual sensation in the joints (Matthews, Waud, Roberts, & Campbell, 2005). Due to their prevalence, it would be reasonable to assume that the symptoms experienced in this study would have been highly expected to occur by many of the participants, thereby appearing more frequently. The implication, therefore, is that the strength of the symptoms rests largely on the specifics of each individual's expectancy regarding lactose consumption, with gut-related symptoms occurring more frequently than systemic ones because occur more frequently in daily life.

Another potential explanation for the lack of significant increases in symptoms other than stomach pain, bloating, and flatulence lies within the physiology of these processes. Although

lactose intolerance seems to have a psychological aspect, it is clear that it has a strong physiological basis. Perhaps the formation of systemic symptoms is simply less influenced by expectancies and relies more on the physiological reaction to lactose. The gut-related symptoms that we found to emerge in this study could not have resulted from a physical reaction to lactose—the concentration within the pill was far below the threshold required for purely physiological symptoms. It may, therefore, be the case that participants did not manifest many systemic symptoms because they did not consume a sufficient quantity of lactose.

Although research specifically comparing these ideas is scarce work on sociogenic illness suggests that many of the symptoms occurring in LI, but not experienced by participants in the present study, can be elicited by expectancies (Lorber, Mazzoni, & Kirsch, 2007). To investigate sociogenic illness, or the condition when an individual discovers that someone else is ill and thereby 'catches' the symptoms himself, researchers randomly selected students to inhale a sham environmental toxin that experimenters described as linked to the most common sociogenic symptoms (e.g., headache). Furthermore, half of each group observed a female confederate who noticeably manifested her symptoms to assess the effects that direct observation, as opposed to simply learning about the symptoms from the experimenter. Participants then recorded their symptom ratings every ten minutes for an hour. Those who inhaled the sham toxin had significantly higher ratings of the described symptoms than controls, who did not. This finding was especially accentuated when women observed the female confederate experiencing symptoms. These results support the hypothesis that expectancy manipulation can result in sociogenic illness, and therefore suggest that systemic symptoms such as headaches can also manifest themselves in response to expectancies. Although far from conclusive, these findings

imply that the results witnessed in the current study are not due to the physiological characteristics of symptoms, but rather stem from the characteristics of the elicited expectancies.

Limitations

A number of limitations affected the current study. The first is the small group of participants recruited—although the sample size included 34 individuals, only six were highly intolerant to lactose. This shortage of participants was problematic, since the relationship between expectancies and symptom formation seemed the most robust for this group; it would have been advantageous to demonstrate the strength of the effect with more such individuals to increase power. Unsurprisingly, recruitment proved difficult—there are few people who would volunteer to experience LI symptoms. Nevertheless, taken as pilot research, these findings are promising. In addition to the small original sample size, a number of participants had misunderstood the pre-expectancy manipulation symptom measure, and rated their usual LI symptoms instead of what they felt at the time. Clarifying the wording of the survey would be beneficial in the future. Finally, when running the full-scale study, researchers may wish to extend the protocol's duration. Although logistical considerations prevented testing beyond a period of 30 minutes, extending the duration of the study to four hours may lead to the effects of expectancies being shown not only for the severely intolerant individuals, but also for low and medium-intolerants. Since symptoms take anywhere between several minutes and four hours to manifest (Harrington & Mayberry, 2008), it is possible that only the highly intolerant expected to experience physiological discomfort almost immediately. Indeed, upon learning that the pill contained lactose, many of the participants noted that they didn't expect to feel the effects for several hours. Since there was no expectancy of an immediate response, but rather of a delayed one, it is not surprising that we found no significant effects for low and medium-intolerant individuals.

Perhaps extending the length of testing to allow for symptom formation over the course of two to four hours would demonstrate a robust effect for all severity groups.

Implications & Future Directions

The finding that expectancies play an important role in LI supports has a number of positive implications. Because were most strongly linked to expectancies for severely intolerant individuals, there may be a way to devise a novel form of therapy for the most severe sufferers of the condition, focusing on managing expectations. Of course, it may also be possible to treat those with lesser degrees of intolerance by managing expectancies; research, however, has yet to show that expectancies play as large a role in their symptom manifestation. There there are no widely effective therapies for LI at the time of writing, but distant prospects of a potential treatment are remain an exciting possibility.

Therapy would, in turn, allow LI individuals to consume more dairy foods. This could provide numerous health benefits, such as reduction in female depression, protection against cancers and ulcers, etc. (Szilagyi, 2002).

Although the optimal outcome of this research would be a treatment for LI, we must first investigate a number of preliminary questions. Firstly, the reasons for the appearance of certain symptoms, but not of others, must be investigated. Specifically, we should determine whether expectancies affect some physiological processes underlying systemic symptoms less than gut-related ones (and bloating in particular), or whether the lower frequency of occurrence for some symptoms witnessed in the current study is a direct result of the expectancies themselves. Secondly, we should determine whether expectancies lead to symptom formation in severe LI

sufferers alone, or whether they result in symptoms for low and medium-intolerant individuals given sufficient time.

Conclusion

This pilot study found that symptoms of lactose intolerance may be induced in participants by manipulating their response expectancies regarding symptom formation, a finding particularly noticeable for bloating and flatulence in highly intolerant individuals. These results lend support to the idea that daily lactose intolerance symptoms may stem from expectancies, rather than physiological factors.

Appendix

Neurocognitive Correlates of Lactose Intolerance

www.tinyurl.com/lact-intolerance

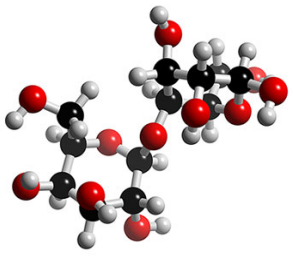
Once you've signed the consent form, please click next to begin the survey

Jewish General Hospital
3755 Cote-Ste-Catherine Rd.
Montreal, Quebec H3T 1E2
Tel.: 514-340-8210

There are 26 questions in this survey

The pill

1
In your case, the pill contains β-D-galactopyranosyl-(1→4)-α-D-glucopyranose:



***

General Information

1. Age: *

Please write your answer here:

2. Gender: *

Please choose **only one** of the following:

- ○Female
- ○Male

3. Do you suffer from, or are currently suffering from, an illness or medical condition apart from lactose intolerance? *

Please choose **only one** of the following:

- ○Yes
- ○No

(If yes, please specify: *

Please write your answer here:

4. Are you currently taking any medication? *

Please choose **only one** of the following:

- ○Yes
- ○No

(If yes, please specify: *

Please write your answer here:

5. How long have you been experiencing symptoms of lactose intolerance? *(e.g.: 7 years, 5 months)* *

Please write your answer(s) here:

- years
- months

6. How strong are your symptoms when you ingest even a very small quantity of lactose (i.e. a teaspoon of milk)? (1 = Barely Noticeable/ 5 = extreme) *

Please choose **only one** of the following:

- ○1
- ○2
- ○3
- ○4
- ○5

7. Have you been tested for lactose intolerance? *

Please choose **only one** of the following:

- ○Yes
- ○No

If yes, how were you tested? *

Please choose **only one** of the following:

- ○Hydrogen Breath Test (blowing into a machine after consuming lactose)
- ○Lactose Tolerance Test (blood sample analyzed to assess levels of glucose after consuming lactose)
- ○Genetic Test (blood sample or cheek swab analyzed by laboratory)
- ○Other

If other:

Please write your answer here:

***

Symptoms

Please describe any symptoms you are experiencing by answering the questions below:

Please describe any symptoms you are currently experiencing:

(1 = Barely Noticeable / 5 = Extreme)

*

Please choose the appropriate response for each item:

	1 = Barely Noticeable	2	3	4	5 = Extreme
Abdominal pain	○	○	○	○	○
Bloating	○	○	○	○	○
Flatulence	○	○	○	○	○
Diarrhea	○	○	○	○	○
Nausea	○	○	○	○	○
Headache	○	○	○	○	○
Loss of concentration	○	○	○	○	○
Unusual sensation in your joints	○	○	○	○	○
Sore throat	○	○	○	○	○

BP1

Please allow the experimenter to check your blood pressure. Once this is done, please click next.

***

Were you aware that β-D-galactopyranosyl-(1→4)-α-D-glucopyranose is commonly used as a placebo? *

Please choose **only one** of the following:

- ○ Yes
- ○ No

***

Blood Pressure

Please allow the experimenter to check your blood pressure once more. Once this is done, please click next. *

***

We would like you to know that β-D-galactopyranosyl-(1→4)-α-D-glucopyranose is one of the chemical names of lactose.
In other words, the pill you have ingested contains lactose.

***

If you have taken PSYC410 with Dr. Amir Raz, please complete a short survey on the adjacent computer before we start to monitor your symptoms.

If the survey is unavailable, please click on the link to watch a video segment:

http://www.cbsnews.com/video/watch/?id=4126233n

***

Please do not touch the computer. The experimenter will advance to the next question for you.

***

Lactose intolerance

4. **Please describe your first negative experience with lactose: ***

Please write your answer here:

2. Who diagnosed your lactose intolerance? (e.g., family doctor, general practitioner, self-diagnosis) *

Please choose **only one** of the following:

- ○ Medical Doctor
- ○ Alternative Practitioner (e.g. herbalist, homeopath, etc.)
- ○ Self-Diagnosis
- ○ Other

If Other, Please Specify: *

Please write your answer here:

3. What was your worst ever experience of lactose intolerance? *

Please write your answer here:

4. What are your typical symptoms of lactose intolerance? *

Please write your answer here:

***

Symptoms

Please describe any symptoms you are experiencing by answering the questions below:

Now that you know the pill you have ingested contains some lactose, please describe once more any symptoms you are experiencing by answering the questions below:

(1 = Barely Noticeable/ 5 = Extreme)

*

Please choose the appropriate response for each item:

	1 = Barely Noticeable	2	3	4	5 = Extreme
Abdominal pain	○	○	○	○	○
Bloating	○	○	○	○	○
Flatulence	○	○	○	○	○
Diarrhea	○	○	○	○	○
Nausea	○	○	○	○	○
Headache	○	○	○	○	○
Loss of concentration	○	○	○	○	○
Unusual sensation in your joints	○	○	○	○	○
Sore throat	○	○	○	○	○

***

BP3

Please allow the experimenter to check your blood pressure for a final time. Once this is done, please click next.

Connecting Text: Pilot study to Study 2

Our review, in combination with the pilot study, lends support to the idea that lactose intolerance symptoms are affected by expectancies. Although the pilot did not include a serious statistical focus, we aim to include such analysis in its published form (as we did with the following paper, published in *Allergy*), which we are submitting for peer-review shortly.

In addition to lactose intolerance, we sought to explore the role of psychology in other conditions which posed a problem for the biologically-centered conception of medicine. Several such conditions exist (e.g., asthma (Wright et al., 1998)), but Montreal is home to number of dermatologists who are involved with the treatment of Chronic Spontaneous Urticaria (CSU), and working with Dr. Ben-Shoshan, who is involved with CSU clinics both at the Jewish General Hospital and the Montreal General Hospital, made CSU seem especially suited to such an investigation.

CSU, an idiopathic variant of hives, only sporadically responds to medication. Moreover, the condition may last for many years, severely decreases quality of life, and leaves both patients and physicians frustrated by its recurrence.

In the following systematic review, we examine the evidence for psychological factors in CSU.

Psychosocial factors and chronic spontaneous urticaria:

A systematic review

Allergy, 68 (2):131-41

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Key Words

Urticaria, psychology, behaviour, psychosocial factors, mind-body interaction

Abstract

CONTEXT: Chronic Spontaneous Urticaria (CSU) is one of the most costly allergic conditions challenging physicians as well as patients and their families. Despite evident lacunae in the understanding of the pathogenesis, at least some findings suggest that psychosocial factors likely contribute to the development and exacerbation of CSU.

OBJECTIVE: To assesses the contributions of psychological factors to CSU in rigorous placebo-controlled randomized clinical trials

DATA SOURCES: Systematic search of PubMed and OVID/Medline databases from January 1, 1935 to January 1, 2012.

STUDY SELECTION: Original research in English, Spanish, and French exploring the association between CSU and psychosocial factors.

DATA EXTRACTION: Two investigators independently reviewed all titles and abstracts to identify potentially relevant articles and resolved discrepancies by repeated review and discussion and arbitration of a third reviewer. Quality of systematic reviews and meta-analyses was assessed using a measure based on the Newcastle-Ottawa Scale and psychological conditions of CSU patients.

DATA SYNTHESIS: We identified 114 eligible studies spanning 77 years and featuring 17 reviews, 67 studies related to neither CSU nor psychosocial factors, and 8 studies which provided either no prevalence estimates or insufficient sample size. Pooling effect sizes using random effects, analyses revealed that, despite large heterogeneity (I^2 of 97.60%), psychosocial factors had a prevalence of 46.09% (95% confidence interval, 44.01%, 48.08%).

CONCLUSION: Future research needs to better establish the contribution of psychosocial factors to the pathogenesis and exacerbation of CSU, and explore the possible benefit of behavioral interventions to the development of new management strategies.

Introduction

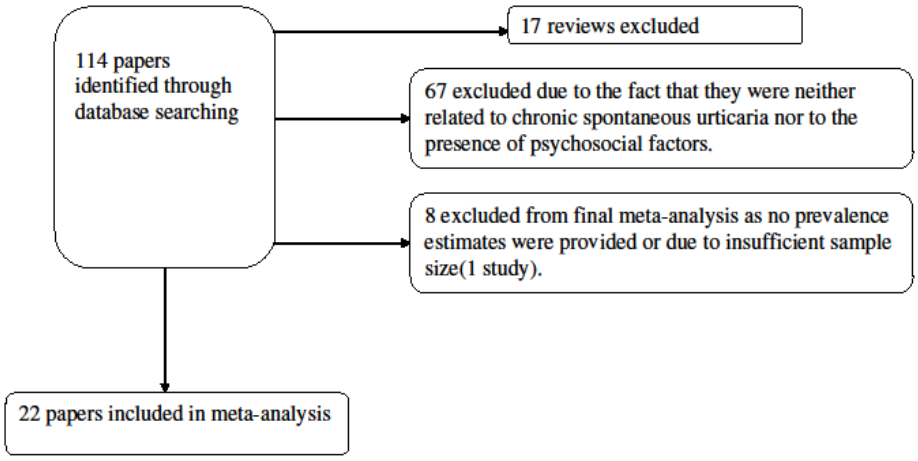
Chronic Spontaneous Urticaria (CSU) is a common and debilitating allergic condition. CSU affects 0.5%-1% of the population typically presenting with transient wheals, which last for at least 6 weeks, sometimes with concomitant angioedema. The pathogenesis of, and effective treatment for, CSU are at best unclear and tenuous, respectively (Zuberbier et al., 2009). Furthermore, because IgE-mediated allergy rarely emerges as an aggravating factor, the conceptualization of CSU should probably weigh less on its notion as an allergic condition and more on the idea of a chronic inflammatory disease (Augey et al., 2011). Whereas many physicians may consider the non-life-threatening symptoms of CSU as relatively mild, most specialists concur that the disfigurement and discomfort associated with this disorder can often pose a serious challenge to the treating clinician and a long-term hardship for patients and their families (Ferrer, 2009). With spontaneous remission occurring in only 30-55% of cases within five years, individuals with CSU often seek multiple consultations with different allergists, dermatologists, and other practitioners in a desperate attempt to relieve their challenging symptoms (Ben-Shoshan, Clarke, & Raz, 2012; Zuberbier et al., 2009). This trend introduces a prolonged burden to the health care system while decreasing the quality of life for individuals with CSU. Compared to the general population, furthermore, individuals with CSU frequently rank in the lowest quartile on physical functioning and below the 20th percentile for items indexing psychological health (Ferrer, 2009). Adults with CSU are absent from work more days than any other group of individuals suffering from allergic conditions; children with CSU perform worse than those without CSU at school (Delong, Culler, Saini, Beck, & Chen, 2008). In this regard, CSU is one of the most costly and poorly controlled allergic conditions. A recent survey examining the controversial influence of psychological factors in CSU showed that the

majority of Canadian allergists reported that psychosocial parameters played a notable role in the pathogenesis of CSU (Ben-Shoshan et al., 2012). In line with previous efforts, the present paper examines how tenable these clinical impressions are by providing a systematic review documenting the involvement of psychological components in CSU and discussing implications for potential therapeutic approaches (Buffet, 2003).

Methods

We first conducted a search of the PubMed and OVID/Medline databases using the keywords "urticaria", "chronic urticaria", "chronic spontaneous urticaria" – given that the definition of CSU was not clearly established in early studies, we also included more general terminology such as urticaria and chronic urticaria but excluded articles clearly assessing physical or acute urticaria – "psychopathology", "stress", "depression", "anxiety" "life events" and "axis I" and "axis II", including full-text accessible articles in English, French and Spanish. We then performed a meta-analysis that included all these studies (see Figure 1) from January 1, 1935 to January 1, 2012. After two reviewers (M.B.S. and I.B.) independently evaluated all potentially relevant studies, we conducted statistical analyses using STATA® version 12 (StataCorp LP, College Station, TX).

Figure 1. Results of search strategy of systematic review and meta-analysis.


114 papers identified through database searching
17 reviews excluded
67 excluded due to the fact that they were neither related to chronic spontaneous urticaria nor to the presence of psychosocial factors.
8 excluded from final meta-analysis as no prevalence estimates were provided or due to insufficient sample size(1 study).
22 papers included in meta-analysis

Methodological quality of included studies

In order to assess the quality of the aforementioned studies, we employed a standardised measure specifically tailored to this systematic review, based on the Newcastle-Ottawa Scale (NOS) (Siegfried et al., 2005). This approach included the appraisal of external and internal validity, as well as biases common to observational studies specific to CSU and psychosocial factors. The independent reviewers mentioned above evaluated study quality separately, and resolved differences in opinion by consulting a third reviewer (A.R.) (Table 1).

Pathogenesis

Whereas mast cells play a role in chronic urticaria, experts rarely consider allergens to be the triggers. Examining IgE sensitization and allergy in 128 adults with chronic urticaria, researchers found that of 105 patients with interpretable skin prick tests, only 46.7% were IgE sensitized (Augey et al., 2011). Two patients had clinically relevant positive skin prick tests, but their chronic urticaria had many other triggering factors, and neither completely remitted after the withdrawal of the implicated allergens. Thus, the authors concluded that although IgE sensitization is higher in chronic urticaria patients than in the global adult population, it does not constitute an expression of an IgE-mediated allergy. Instead, the authors suggest the possibility of a chronic inflammatory disease, more frequent in IgE sensitized individuals and favoured by multiple factors, among which the IgE-mediated allergy is exceptional.

Patients with CSU comprise at least two subgroups: those truly idiopathic, and those who had been previously diagnosed with idiopathic disease but who later turned out to have autoimmune CSU – approximately 40–50% of adults and children (Sahiner et al., 2011). Allergists often characterize the latter, autoimmune CSU, by a positive autologous intradermal injection test (Sabroe et al., 1999) wherein functional mast cells are stimulated by IgG antibodies towards the

alpha chain of the high-affinity IgE receptor, and rarely, towards IgE itself (Wedi, 2008); the former group is a diagnosis by exclusion .

In line with an unclear pathogenesis, conundrums persist regarding potential triggers of CSU. For example, some clinicians maintain that infections are triggers despite evidence showing little, if any, association between CSU and infections (e.g., bacterial, viral, parasitic) in both children and adults (Sahiner et al., 2011). Similar confusion lingers concerning psychological components. Although many practitioners concur that psychosocial factors are likely contributors to the exacerbation of symptoms in existing CSU, some experts largely dismiss the involvement of psychological parameters in the onset, and even manifestation, of CSU; yet the overwhelming tenor from many allergists intimates that psychological factors play a role in the pathogenesis of this condition (Ben-Shoshan et al., 2012).

Results of meta-analysis related to potential psychopathology in CSU

Clinicians have long speculated the presence of an association between psychological factors and CSU (Chung, Symons, Gilliam, & Kaminski, 2010a; Stokes, 1940); however, reports elucidating this relationship are both scantily available and methodologically weak. Tables 1 and 2 list 30 such studies – 15 employing a case-control design and 15 using cross-sectional methods – and provide a brief description of their gist. The majority of these studies examined the effect of psychosocial factors through prevalence estimates (Anasagasti, Peralta, Harto, Chinchilla, & Ledo, 1986; Badoux & Levy, 1994; Barbosa, Freitas, & Barbosa, 2011; Berrino et al., 2006; Chung et al., 2010a; Fava, Perini, Santonastaso, & Fornasa, 1980; Graham & Wolf, 1950; Hashiro & Okumura, 1994; Herguner et al., 2011; Juhlin, 1981; Malhotra & Mehta, 2008; Maniaci, Epifanio, Marino, & Amoroso, 2006; Miller, Freeman, & Akers, 1968; Ozkan et al., 2007; Pulimood, Rajagopalan, Rajagopalan, Jacob, & John, 1996; Sheehan-Dare, Henderson, &

Cotterill, 1990; Shoemaker, 1963; Silvares, Coelho, Dalben, Lastoria, & Abbade, 2007; Staubach et al., 2011; Stokes et al., 1935; Uguz, Engin, & Yilmaz, 2008; Wittkower, 1953), with a single study providing the odds ratio for the this effect (Yang, Sun, Wu, & Wang, 2005). Five studies assessed the effect through differences in quantitative measures of psychosocial factors (Engin, Uguz, Yilmaz, Ozdemir, & Mevlitoglu, 2008; Pasaoglu, Bavbek, Tugcu, Abadoglu, & Misirligil, 2006; Sengupta, 1982; Sperber, Shaw, & Bruce, 1989; Vargas Laguna, Pena Payero, & Vargas Marquez, 2006), one study involved only three patients with CSU (Bashir, Dar, & Rao, 2010) and one explored the function of the hypothalamic-pituitary-adrenal axis hormones as well as basophile activation, in the link between psychological stress and CSU (Dyke, Carey, & Kaminski, 2008). Altogether, we included 22 studies in our meta-analysis, assessing the prevalence of psychosocial factors in CSU patients. The majority of these studies failed to control for potential confounds, and a substantial percentage neglected to measure psychosocial factors by way of a validated test (prevalence estimates summarized in Table 2 and Figure 2). The studies that did use standardized methods largely relied on interviews, such as the Structured Clinical Interview for DSM-III/IV Axis I&II (SCID-I/SCID-II) (Uguz et al., 2008) and the mini International Diagnostic Interview for Mental Disorders (mini-DIPS) (Staubach et al., 2011) in combination with questionnaires such as the Hospital Anxiety and Depression Scale (HADS) (Staubach et al., 2011), the Beck Depression Inventory (BDI) (Sheehan-Dare et al., 1990), and the Symptom Checklist-90 Revisited (SCL-90R) (Staubach et al., 2011). Such measures permit researchers to rigorously examine a broad range of psychological parameters. The pooled prevalence of psychosocial factors was 46.09% (95% CI, 44.01%, 48.08%) with an I^2 of 97.60%, reflecting the high heterogeneity amongst studies.

Several of the aforementioned studies report on the involvement of socio-cognitive factors in the exacerbation of urticaria. Historically, early studies reported that psychological factors were important in urticaria cases (Broom, 2010; Stokes, 1940). Later, a study examining 40 individuals who experienced bouts of urticaria for at least three months found that the majority of patients suffered from psychopathology – largely anxiety and depression – and responded favourably to psychotherapy (Shoemaker, 1963) (Intimating that a generic emotional theme was too simplistic an explanation for CSU, the study concludes that "chronic urticaria can be best understood as a physical reaction to a condensation of biological and psychological elements arising out of the personal history of an individual under the stress of a particular set of life circumstances" (p. 365).) More recent studies reveal that, when compared to controls with no medical history of chronic hives, individuals suffering from CSU had worse co-morbidity, higher levels of stress related to either perceived events or actual life experiences (Chung, Symons, Gilliam, & Kaminski, 2010b; Dyke et al., 2008; Graham & Wolf, 1950; Juhlin, 1981; Wittkower, 1953). Table 2 provides a comprehensive list of studies reporting that, compared to a healthy control group, individuals with urticaria had significantly higher scores on measures of somatization, obsessive-compulsive disorder, interpersonal sensitivity, and depression, anxiety (Barbosa et al., 2011; Engin et al., 2008; Ozkan et al., 2007; Sperber et al., 1989); insomnia (Yang et al., 2005); and stressful life events (e.g., death of a close family member) (Malhotra & Mehta, 2008).

Caveats and Limitations

Over the span of 77 years, methodologies and diagnostic approaches have changed substantially. Given that this systematic analysis assesses different types of psychopathologies, pooled estimates may reflect disparate prevalence estimates of specific psychosocial process in patients

with CSU. Given the wide range of estimates (16% (Malhotra & Mehta, 2008) to 96% (Graham & Wolf, 1950)) and sparse data documenting psychopathology in CSU, we provide a rough index for the involvement of psychopathological component in these patients. These factors may be a consequence of, rather than a cause for, CSU (e.g., anxiety and depression often coexist with chronic pain (Greenberg, 2012) and other disease groups, including chronic skin conditions (Zirke et al., 2012)). This chicken-or-egg conundrum, wherein clinicians struggle to unravel whether psychosocial factors precede or follow CSU, remains a conceptual obstacle to understanding the mental and behavioral components in the symptomatology. The putative role of psychosocial factors may or may not cause CSU; however, given their presence in nearly 50% of patients, management approaches – especially those aiming to control psychosocial components – may constitute a substantial boon to individuals with CSU. Finally, publication bias remains a possibility (i.e., while we report a high prevalence, findings showing low prevalence may remain unpublished due to a file drawer effect).

Table 1. Methodological quality of included studies.

tudy	External validity		Internal validity								
			Performance (of exposure=CSU)		Detection (of outcome)		Attrition	Selection bias/control for confounding			
	Representative[†]	**Participation rate**[††]	**Clear definition of CSU**	**Exclusion of cases with identifiable trigger**	**Use of validated measure to define psychopathology**	**Blinded assessors**	**Completeness**[‡]	**Age**	**Sex**	**Presence of autoimmune diseases**	**Presence of atopy**
tokes CS)	NS	NS	_	_	_	_	NS	_	_	_	_
raham CS)	NS	NS	_	_	_	_	✓	_	_	_	_
Vittkower CS)	NS	NS	_	_	_	_	NS	_	_	_	_
hoemaker S)	NS	NS	_	_	NS	_	NS	_	_	_	_
ava CS)	NS	NS	✓	✓	✓	_	NS	_	_	_	✓
Miller CS)	NS	NS	_	_	_	NS	NS	_	_	_	_
uhlin (CS)	NS	NS	✓	✓	_	NS	NS	_	_	_	_
perber (CC)	NS	NS	✓	NS	✓	_	NS	_	_	_	_
engupta (CS)	✓	NS	✓	NS	✓	NS	NS	_	_	_	_
nasagasti CS)	NS	NS	_	NS	✓	NS	NS	✓	✓	_	_
heehan-Dare C)	NS	NS	✓	✓	✓	NS	NS	✓	✓	_	_
adoux_1 CS)	NS	NS	_	_	✓	NS	NS	_	✓	_	_
adoux_2 CS)	NS	NS	_	_	✓	NS	NS	_	✓	_	_
lashiro CC)	NS	NS	✓	NS	✓	_	NS	_	_	_	✓
ulimood CS)	NS	✓	_	NS	✓	NS	NS	_	_	_	_
ang CC)	NS	NS	✓	✓	✓	✓	NS	✓	✓	✓	✓
errino CS)	NS	✓	✓	✓	✓	NS	NS	_	_	_	_
laniaci CC)	NS	NS	✓	✓	✓	NS	NS	_	_	_	_
asaoglu CC)	NS	NS	✓	✓	✓	NS	NS	_	_	_	✓
argas	NS	NS	_	NS	✓	NS	NS	_	_	_	_

)zkan (CC)	NS	NS	✓	✓	✓	NS	NS	_	_	✓	✓
guz C)	NS	NS	✓	✓	✓	NS	NS	_	_	✓	✓
lvares (CS)	NS	NS	NS	NS	_	NS	NS	_	_	_	_
alhotra (CS)	NS	NS	NS	NS	✓	NS	NS	_	_	_	_
ugin (CC)	NS	NS	✓	✓	✓	NS	NS	_	_	✓	✓
/ke C)	NS	NS	✓	✓	_	_	✓	_	_	_	_
ashir (CS)	NS	NS	_	✓	✓	NS	NS	_	_	_	_
hung (CS)	NS	✓	✓	✓	✓	NS	✓	_	_	✓	NS
ergüner (CC)	NS	NS	✓	✓	✓	NS	NS	✓	✓	_	_
aubach (CS)	NS	✓	_	✓	✓	NS	✓	_	_	✓	_
arbosa (CC)	NS	✓	✓	✓	✓	NS	✓	_	_	_	_

CS=cross sectional study. CC=case control study; OR=odds ratio; ✓indicates the measure was adequately addressed in the study; NS= not specified.

[†]Studies received a✓ if the sample included all eligible CU patients over a defined period of time, or in a defined catchment area, or a random or systematic sample of these;

[††] Studies received a ✓ if the percentage participation was 80% or more;

[‡] Studies received a ✓ if the percentage of participants in the final analysis was 80% or more of the original sample, or if a full description of those lost-to-follow-up was not suggestive of bias. For selection bias/control of confounding a ✓ indicates that the group variable was either balanced between groups (10% or less difference) or adjusted for during the analysis.

** Reported significantly higher scores for psychiatry disorders but no OR nor prevalence estimates provided.

*** OR for this study were used to assess the effect of psychopathology.

****This study explored the effect of stress on basophil function in CSU patients and did not assess the prevalence of psychosocial factors in these patients.

***** Only 3 patients with chronic urticaria were recruited.

******For severe/moderate anxiety

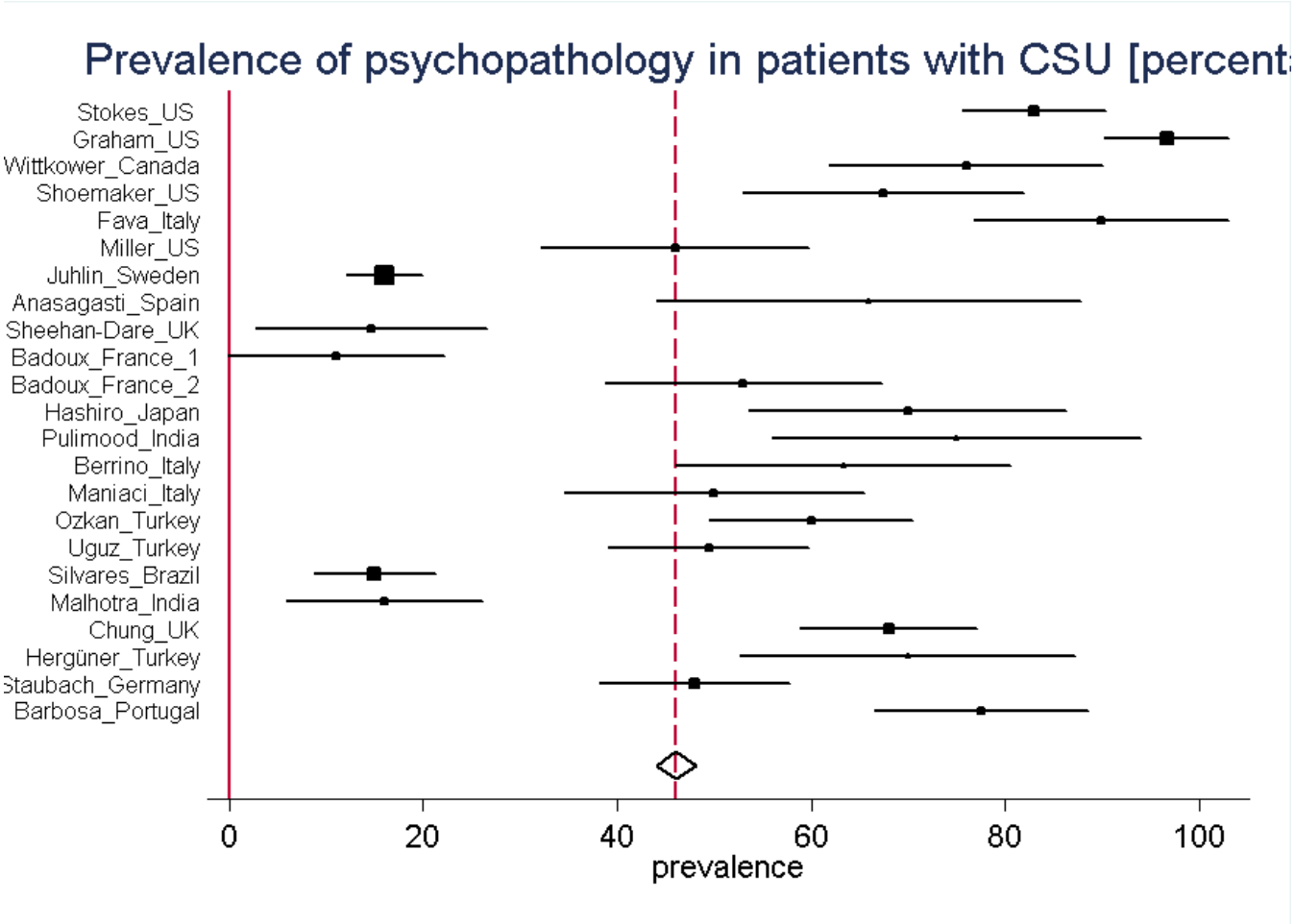
Table 2. CSU and psychosocial factors.

Study	Publication year	Country	Study design	Sample size	Effect
Stokes	1935	US	Cross- sectional	100 individuals with CSU	Abnormal psychoneurogenous elements appeared in the background of 83% urticaria cases, as compared with 24% in a control series of cases of psoriasis, acne, and impetigo.
Graham and Wolf	1950	US	Cross- sectional	30 individuals with urticaria	In 29 of 30 patients studied, there was an almost invariable relationship between a particular attitude and attacks of urticaria. The majority of urticaria attacks occurred at times of helpless resentment.
Wittkower	1953	Canada	Cross- sectional	35 individuals with urticaria/ angioneurotic edema	Two-thirds of the patients in this series spontaneously stated that they missed parental, and especially maternal affection, as children. Events such as desertion or impending desertion by husband, wife, or sweetheart; impotence of the husband; or departure of the husband for service abroad were among the incidents preceding the onset of urticaria in 19 of 25 urticaria patients.
Shoemaker	1962	US	Cross-sectional	40 individuals with urticaria	13 of 40 patients were defined as socially normal.
Miller	1968	US	Cross-sectional	50 individuals with urticaria lesions for more than 8 weeks. Included were those for whom food, inhalants, infections, and physical factors were associated with chronic urticaria, as well as those with vasculitis, mastocytosis and malignancies.	23 of 50 patients had emotional factors associated with urticaria
Fava	1980	Italy	Cross-sectional	20 individuals with urticaria present more than 3 months	18 patients with chronic urticaria reported at least one stressful life event before illness onset.
Juhlin	1981	Sweden	Cross- sectional	330 consecutive patients with recurrent urticaria of 3 months to 40 years duration	Severe psychiatric problems were mentioned by 16%.
Sperber	1989	US	Cross- sectional	19 outpatients with CSU	Urticaria patients, when compared to healthy controls, revealed substantially higher scores (based on SCL-90) on scales of somatization, obsessive-compulsive disorder, interpersonal sensitivity, depression, and anxiety.
Sengupta	1982	India	Cross-sectional	40 patients with CU	Emotional liability and sense of insecurity but no estimates or score provided.
Anasagasti	1985	Spain	Cross-sectional	18 patients with CU	Existence of abnormal personality factors - submission and dependence - in 61% and 66% of patients, respectively.
Sheehan_Dare	1990	UK	Cross-sectional	34 patients with CSU	14.7% of patients with CSU had depressive symptoms vs. 4.4% of controls, although difference did not reach significance.
Badoux group 1	1994	France	Cross –sectional	27 men	11% had elevated scores of psychological symptoms.
Badoux group 2	1994	France	Cross –sectional	47 women	53% had elevated scores of psychological symptoms
Hashiro	1994	Japan	Case control	30 outpatients with CSU and 39 normal controls	Psychologically positive responses to any one of three psychological tests were seen in 70% of the chronic urticaria patients, but in only 25.6% of the controls.

					These differences were statistically significant ($p < 0.01$).
Pulimood	1996	India	Cross –sectional	20	The highest rates of psychiatric morbidity were found in patients with CU (75%).
Yang	2005	Taiwan	Case control	75 patients with CSU and 133 controls with tinea pedis	Patients with CSU had significantly more stressful life events and more severe insomnia.
Berrino	2006	Italy	Cross-sectional	30 subjects with CSU	Most of the patients experienced a "stressor" event within the six months before the onset of CSU.
Maniaci	2006	Turkwy	Cross sectional	40	CIU patients had higher alexithymia levels ($p < .05$) on comparison to the normal population.
Pasaoglu	2006	Turkey	Cross sectional	59 CSU patients and 59 controls	Scores for hypochondriasis, depression, hysteria, psychopathic deviance, paranoia, psychasthenia, schizophrenia, and social introversion were higher in patients with CIU compared to the control group ($P < 0.05$).
Vargas	2006	Spain	Cross sectional	29CSU patients	Chronic urticaria, had a significantly higher anxiety state when compared to control.
Ozkan	2007	Turkey	Case control	84 CSU patients and 75 controls	A psychitric diagnosis was given to 60% of the patients, with depressive disorders being the most prevalent (40%). Most patients (81%) believed that their illnesses were due to stress.
Uguz	2007	Turkey	Case control	89 CSU patients and 60 controls	Of patients with CSU, 44 (49.43%) had at least one Axis I diagnosis, and 40 (44.9%) had at least one personality disorder. The most common Axis I disorder was obsessive–compulsive disorder (25.84%), and the most common Axis II disorder was obsessive–compulsive (30.33%) personality disorder.
Silvares	2007	Brazil	Cross- sectional	125 CSU patients	15% reported stress as the main trigger.
Malhotra	2008	India	Case control	50 CU, and 50 psoriasis patients	16% of CU patients had stressful life events (mainly death of a close family member) occur within a year prior to onset of symptoms.
Engin	2008	Turkey	Case control	73 patients with CSU, and 34 healthy subjects	Beck Depression Inventory and the Beck Anxiety Inventory were significantly higher in CSU patients
Dyke	2008	UK	Case control	30 patients with CSU and 30 normal controls	Both corticotrophin releasing factor (CRF) and adrenocorticotrophic hormone (ACTH) were shown to activate basophils. The mean increase in the percentage of basophils expressing CD63 was 24.5% (95% CI, 21.8,27.2%) for the CSU patients and 10.8% (95% CI = 8.9–12.7%) for the volunteer controls.
Bashir	2010	Pakistan	Cross sectional	3 patients with CU	2 out of 3 with chronic urticaria had depression.
Chung	2010	UK	Case control	100 CSU, and 60 allergy patients	Compared to allergy patients, CSU patients had worse co-morbidity, and higher levels of life event stress and perceived stress. Emotion-focussed coping was associated with severity of CSU
Hergüner	2011	Turkey	Case control	27 children with CSU and 27 age and sex matched controls	The study group had more frequent psychiatric diagnoses than the control group (70% vs. 26%, p=0.002) and the most common psychiatric disorders were social anxiety disorder
Staubach	2011	Germany	Cross-sectional	100 individuals referred to a dermatological inpatient clinic over a period of 20 months for the diagnostic evaluation of CSU	48% patients with CSU were found to have one or more mental disorders as assessed by diagnostic interviews and mini-DIPS.
Barbosa	2011	Portugal	Case control	55 CSU patients and 31 controls	76.64% of CSU patients reported moderate/severe anxiety symptoms vs. 29% of controls. There was a significant statistical difference between CSU patients and the control group for anxiety symptoms scores ($\chi 2 = 4.966$; $p < 0.026$ and $t = 5.574$; $p < 0.0001$).

OR=odds ratio; RR=relative risk; CI=confidence interval;

Figure 2. Prevalence (in percentage) of psychosocial factors in patients with CSU. *†



***Only studies reporting prevalence estimates were included.**

†Pooled estimate = 46.09% (95% CI, 44.01%, 48.08%); (I^2 = 97.60%)

Physiological mechanisms: bridging psychological factors with CSU

Several reports suggest that CSU may emerge through interactions between the nervous and immune systems (Theoharides et al., 1998). Symptoms result from mast cell activation, elicited through channels such as the hypothalamic–pituitary–adrenocortical axis (Theoharides et al., 1998), the sympathetic and adrenomedullary system (Kasperska-Zajac, 2011), and local skin nerve fibres (Theoharides et al., 2004).

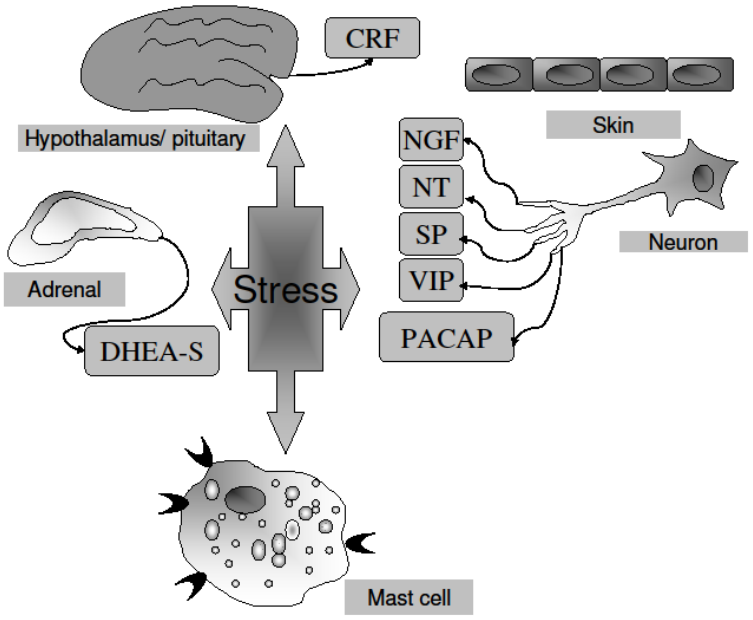
Other studies propose that stress-related mechanisms provide links to CSU. Animal models have shown that acute psychological stress results in cutaneous mast cell activation and links to the expression of corticotrophin-releasing factor (CRF) receptors (Theoharides et al., 2004). Although these receptors selectively release cytokines and other pro-inflammatory mediators, findings suggest that administering anti-CRF prior to stress may inhibit mast cell activation (Theoharides et al., 1998). Human in vitro studies, examining basophil activation and serum cortisol concentrations as indications of stress, also reveal that basophiles in CSU patients have heightened responses to CRF as well as adrenocorticotropic hormone, and that CSU patients manifest higher levels of serum cortisol (Dyke et al., 2008). Moreover, both the main CRF-R subtype in the human skin, CRF-R1, and histidine decarboxylase – the mast cell related gene regulating the production of histamine – manifest more frequently in CSU than in normal foreskin, breast skin, and cultured human keratinocytes (Papadopoulou, Kalogeromitros, Staurianeas, Tiblalexi, & Theoharides, 2005).

Neuroendocrine mechanisms may also link psychological parameters to CSU exacerbation. Persons with CSU exhibit substantial decrease in Dehydroepiandrosterone as well as in its sulfate derivative (DHEA-S). Whereas we know that the nervous system regulates the

homeostasis of the immune system wherein DHEA-S plays a role, it remains unclear whether lower circulating concentration of DHEA-S represents a primary phenomenon on its own or a secondary process associated with the illness-response of different systems (i.e., bearing no direct contribution to the pathogenesis of urticaria) (Kasperska-Zajac, 2011).

Direct interactions between mast cells and local skin nerve fibres pose another potential conduit for the emergence of CSU. Animal models reveal that neural stimulation, resembling stress, leads to the secretion of many neuropeptides capable of triggering mast cells, including substance P (SP), nerve growth factor (NGF), neurotensin (NT), pituitary adenylate cyclase activating polypeptide (PACAP) and vasoactive intestinal peptide (VIP) (Theoharides et al., 2004).

Figure 3. Neuropeptides and hormones capable of activating mast cells.



CRF=corticotrophin-releasing factor; DHEA-S=Dehydroepiandrosterone sulfate; SP=substance P; NGF=nerve growth factor; NT=neurotensin; PACAP=pituitary adenylate cyclase activating polypeptide; VIP=vasoactive intestinal peptide.

Conclusion and future directions

CSU is a frequently occurring skin condition, associated with a severe societal burden and sorely lacking in effective treatment. In addition to our recent survey, indicating that almost 80% of Canadian allergists are of the opinion that psychological factors play a role in the pathogenesis of CSU (Ben-Shoshan et al., 2012), here we show that meta-analytic findings support the high prevalence of co-morbidity between psychosocial factors and CSU. Although the high heterogeneity of the studies surveyed herein precludes a definitive conclusion (I^2 = 97.60%), our pooled prevalence estimate of psychosocial factors in symptomatic patients suggests that such factors comprise close to 50% of CSU cases [46.21% (95% CI, 44.21%, 48.20%)]. Given that

most studies exploring the role of psychological factors are either cross sectional (Berrino et al., 2006; Fava et al., 1980; Graham & Wolf, 1950; Juhlin, 1981; Shoemaker, 1963; Staubach et al., 2011; Stokes, 1940; Stokes et al., 1935; Wittkower, 1953) or traditional case control studies (Barbosa et al., 2011; Chung et al., 2010a; Dyke et al., 2008; Hashiro & Okumura, 1994; Ozkan et al., 2007; Uguz et al., 2008; Yang et al., 2005), future research should include randomized controlled trials, which would allow researchers to establish the effectiveness of behavioral interventions to treat psychosocial parameters. Even if psychological symptoms develop subsequent to CSU and play little or no part in its pathogenesis, the positive correlation between the disease and markers of poor psychological wellness (e.g., anxiety, alexithymia, and low quality of life) indicates that psychotherapeutic treatments and behavioural interventions aimed at alleviating these problems may prove beneficial (Barbosa et al., 2011).

Findings show that suggestion and expectation can have beneficial effects in a number of clinical conditions (Raz, Zephrani, Schweizer, & Marinoff, 2004), including in common dermatological conditions such as warts (Spanos, Williams, & Gwynn, 1990; Surman, Gottlieb, Hackett, & Silverberg, 1973). Such therapeutic suggestions can help control harmful habits, improve symptoms, and provide both immediate and long-term relief (Broom, 2010). Only two studies, however, have explored the role of suggestion in CSU. In the early 1960s, researchers used hypnosis with relaxation therapy in 15 adults with chronic urticaria, reporting that lesions cleared in six patients within 14 months, and improved in eight patients; 80% of subjects, moreover, reduced their intake of medication (Shertzer & Lookingbill, 1987). In line with these results, a case study found that specific self-talk and relaxation techniques had significantly eased symptoms of urticaria in a young woman (Fried, 2002). Incorporating behavioural intervention techniques in the management of CSU, therefore, holds great potential to assuage

symptoms and reduce the use of drugs with potential side effects. Given the clinical impressions of allergists (Ben-Shoshan et al., 2012), the high value of heterogeneity, indexed by I^2 and suggesting that the studies included in the present meta-analysis are difficult to compare, and the lack of effective pharmacological treatment options (Ferrer, 2009), randomized controlled trials exploring the benefits of psychological interventions in CSU are overdue. Establishing the efficacy of such potential interventions would be an enormous boon to patients, free up considerable medical resources, and offer substantial financial savings as a function of reducing both direct and indirect expenses.

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Figure legends:

Figure 1. Results of search strategy of systematic review and meta-analysis.

Figure 2. Prevalence (in percentage) of psychosocial factors in patients with CSU. *†

***Only studies reporting prevalence estimates were included.**

†Pooled estimate = 46.09% (95% CI, 44.01%, 48.08%); (I^2 = 97.60%)

Figure 3. Neuropeptides and hormones capable of activating mast cells.

CRF=corticotrophin-releasing factor; DHEA-S=Dehydroepiandrosterone sulfate; SP=substance P; NGF=nerve growth factor; NT=neurotensin; PACAP=pituitary adenylate cyclase activating polypeptide; VIP=vasoactive intestinal peptide.

Connecting Text: Study 2 to Commentary Response 1

Our explorations of both lactose intolerance and CSU suggest that psychology plays important roles in both conditions. Whereas lactose intolerance symptoms seem to be affected by expectancies, CSU appears to result, in part, from psychological stressors. The cognitive response which accompanies stressful situations often leads to physiological changes. Such cognitive patterns are not inborn, but develop overtime, and may be placed under the rubric of automatic processes—responses so ballistic that they were formerly thought almost impossible to alter consciously (Lifshitz, Aubert Bonn, Fischer, Kashem, & Raz, 2012). Research suggests that these automatic cognitions may be mitigated, thereby reducing stress (Stanley, Schaldach, Kiyonaga, & Jha, 2011).

The following commentary response considers evidence for de-automatizing such processes, and suggests that, in addition to the relaxation therapy suggested in the systematic review, de-automatizing stress responses through hypnosis may prove useful to CSU sufferers.

Commentary Response 1

Converging Evidence for De-Automatization

Consciousness & Cognition, 21(3), 1579-1582.

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At least for some individuals, suggestion seems capable of easing certain automatic processes back into the purview of control. Unrelated to hypnosis and suggestion, a number of accounts have challenged the automaticity of the Stroop effect, demonstrating reduction of Stroop interference (Besner, 2001; Besner and Stolz, 1999a, 1999b, 1999c; Besner et al., 1997; Dishon-Berkovits and Algom, 2000; Kuhl and Kazén, 1999; Long and Prat, 2002; Melara and Algom, 2003; Pansky and Algom, 2002). Furthermore, as Kihlstrom (2011) acknowledges and as we expound on elsewhere in this issue (Lifshitz, Campbell & Raz, 2012), findings from meditative practices coincide with the effects of suggestion on Stroop performance. In this paper we review converging evidence from multiple independent groups of researchers replicating the removal of Stroop interference as a function of suggestion, and expound on nuances of nomenclature regarding suggestibility (Kihlstrom, 2011).

In line with our own results using a classic Stroop paradigm (Raz, 2004; Raz & Campbell, 2011; Raz, Fan, & Posner, 2005; Raz, Kirsch, Pollard, & Nitkin-Kaner, 2006; Raz et al., 2003; Raz, Moreno-Iniguez, Martin, & Zhu, 2007; Raz, Shapiro, Fan, & Posner, 2002), several independent groups have also reported reduced Stroop interference following suggestion. Casiglia and colleagues (2010), for example, reproduced our findings showing that a posthypnotic suggestion for "alexia" reduced the word-color Stroop interference effect in highly suggestible individuals (HSIs). Furthermore, research groups from Italy (Augustinova & Ferrand, 2012) and England (Parris, Dienes, & Hodgson, 2012) have recently reported data supporting Stroop de-automatization as a function of suggestion. In addition to these contemporary accounts, an esoteric report by Sun (1994), written in Chinese, examined the

influence of suggestion on Stroop performance. Following a hypnotic induction, HSIs and LSIs performed a Stroop task with and without the following suggestion:

You are now focusing on the monitor before you. When you see the colored stimulus, do not pay attention to the whole stimulus; focus your vision and attention to the bottom right corner. At this moment, you will only be seeing one color stimulus. Try to identify the color you see as quickly and as accurately as possible. You will definitely be able to complete this task. Are you ready? Alright, let's begin.

Although the above suggestion differs substantially from the instructions we have typically employed in our own work on these topics (e.g., Raz, 2002), Sun (1994) anticipated our findings by documenting that the suggestion significantly reduced the Stroop interference effect for HSIs but not for LSIs. In normal waking consciousness, however, suggestion brought about a difference between HSIs and LSIs neither in the Stroop effect (incongruent minus congruent) nor in Stroop interference (incongruent minus neutral). Such findings contrast with reports, including from our own laboratory (Raz et al., 2006) and from an as yet unpublished independent account (Parris & Dienes, unpublished), indicating that suggestion reduces the Stroop effect in HSIs even in a non-hypnotic context. Thus, although the specific role of the hypnotic induction remains unclear, numerous independent reports converge on the notion that suggestion can reduce the Stroop effect in HSIs.

Single-case studies and anecdotal accounts further support the removal of Stroop interference at the individual level. Although multi-participant experiments provide the gold standard for psychological and medical research, single-case reports may serve to elucidate individual nuances and custom tailor cognitive and therapeutic interventions (Gabler, Duan,

Vohra, & Kravitz, 2011; Kravitz et al., 2009). One study investigating a single highly suggestible face-colour synaesthete, for example, demonstrated reduced involuntary perceptual integration along with alterations in event-related brain potentials as a function of posthypnotic suggestion (Terhune, Cardeña, & Lindgren, 2010). In addition, anecdotal clinical case-studies (Schatzman, 1980), N-of-1 experimental accounts (MacLeod & Sheehan, 2003), and informal unpublished reports (e.g., Thalia Wheatley, personal communication, November, 2002) corroborate the removal of Stroop interference as a function of suggestion.

Beyond the Stroop paradigm, other studies using posthypnotic suggestion demonstrate how putatively automatic processes are amenable to cognitive control. Examples include overriding the flanker compatibility effect (Iani, Ricci, Gherri, & Rubichi, 2006) and the Simon interference effect (Iani, Ricci, Baroni, & Rubichi, 2009). Unpublished data from our laboratory, moreover, indicate that such de-automatization may extend to cross-modal perceptual integration in the McGurk illusion (McGurk & MacDonald, 1976), and that particular suggestions may allow specific individuals to shift automaticity in the opposite direction – rendering difficult tasks more effortless without practice. Collectively, therefore, such converging findings highlight the presence of a robust empirical effect and pave the road to further experimental and clinical applications.

In his commentary, Kihlstrom (2011) points out that while we screened participants using the Harvard Group Scale of Hypnotic Susceptibility (HGSHS:A) (Shor & Orne, 1962) – an index traditionally used to sort individuals into high and low "hypnotizable" categories – we label our participants instead as highly- and less- "suggestible" individuals. In light of the various subtypes of suggestibility (e.g. primary, secondary, placebo), Kihlstrom suggests that we refrain from implying that a singular subtype underlies the observed effects and encourages us to

employ the standard label of "hypnotizability". Whereas we acknowledge the importance of clarifying the notion of suggestibility, the term hypnotizability may carry its own set of problems. These difficulties stem from the operational definition of hypnosis as the administration of an initial suggestion to enter hypnosis (i.e., an "induction" ritual). Although hypnotizability traditionally refers to responsiveness to suggestion following an induction, this definition is problematic given that responses to suggestions in a hypnotic context correlate strongly with responses to the same suggestions outside of hypnosis (Kirsch & Braffman, 2001). Furthermore, induction procedures appear to only slightly enhance response to suggestions (Kirsch et al., 2011). Thus, because hypnotizability scales do not compare responses to suggestions within and outside of a hypnotic context, they may provide a better index of response to suggestion in general than response to hypnotic induction in particular (Weitzenhoffer, 1980). In light of such caveats, some researchers propose that we should reserve the term "hypnotizability" for labeling the degree to which hypnotic induction influences individual responsiveness to suggestions (Braffman & Kirsch, 1999). According to this perspective, the term "hypnotic suggestibility" most accurately designates responsiveness to suggestions following a hypnotic induction.

While terminological debates persist and researchers actively strive to iron out useful operational definitions of hypnotizability and suggestibility (Kirsch et al., 2011), dwelling on such nomenclature may represent a nuanced discussion within the purview of but a few specialists. In our writings we often use these terms interchangeably because we feel that for the larger community of non-experts, such refined shades of meaning may obfuscate more than explain (Raz, 2007). As researchers interested in advancing the science of suggestion and attention, it would behoove us to focus our efforts on clarifying empirical questions and refining

experimental paradigms. In this spirit, independent replications of our Stroop findings and related de-automatization effects provide converging evidence for a robust phenomenon worthy of future investigation.

Connecting Text: Commentary 1 to Paper 3

The heretofore-presented manuscripts point to the importance of psychological variables in conditions we often consider through an exclusively biological perspective. Although I have presented work specifically dealing with CSU and LI, I hope that I have demonstrated the weight that psychological factors may have in conditions typically labeled as purely biological. Of course, while psychological factors play different roles, from great to minimal, in all conditions, the message of import is that we must take such variables into consideration when dealing with other forms of pathology. The medical field is becoming ever-more aware of psychosocial parameters' impact on illness, and my hope is that the findings of this thesis will be applied in the form of general models of biological and psychological interactions. Nevertheless, having thus established the need to address the mental dimension in conditions such as LI and CSU, as well as an idea for more general frameworks, we are faced with an ethical dilemma.

Placebo would appear to be the ideal mechanism for treating the psychologically derived aspects of physiological illness. Inert therapies, such as sugar pills, are already frequently used by clinicians for patient relief, and provide benefits in both cost and time of treatment (Nitzan & Lichtenberg, 2004). In spite of these benefits, the vast majority of placebo administration relies on deception, with clinicians omitting discussing them with the patient. Critics, therefore, level the charge of paternalism against proponents of placebos in the clinic, noting that such deception in the medical context violates patient autonomy (Miller & Colloca, 2009). In spite of recent results suggesting that open-label placebos remain effective (Kaptchuk et al., 2010), current scientific consensus appears to converge on the idea of deception as necessary (Campbell & Raz, 2011). Thus, a palpable tension emerges between a patient's right to autonomy and a clinician's imperative of beneficence.

Before devising a placebo-centered therapy, we must assess whether deceptive placebos are ethically viable. In the following manuscript (Ignorance is bliss: Pre-determined informed consent for deceptive placebo use in clinical practice), I outline both a philosophical and practical framework for the use of deceptive placebos in clinical practice.

Paper 3

Ignorance is bliss:

Pre-determined informed consent for deceptive placebo use in clinical practice

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Abstract

Although placebos have played a major role in clinical practice for the majority of medical history, their use remains a controversial topic. On the one hand, physicians must treat their patients with beneficence, and emphasize their health above all else. If placebos hold benefit for the patient, their use is not only acceptable, but desirable. On the other hand, however, the deceptive practices which characteristically accompany placebo use in the clinical setting encroach on patient autonomy. Using placebos without the patient's consent, let alone awareness, harkens back to the paternalistic medical practices of the early 20th century.

In the United States, the American Medical Association's recommendations on the topic of placebo use are both vague and dated. First, I will discuss these recommendations, and outline the present state of the deceptive placebo debate. I also note the most notable proposed solutions to this problem, and discuss their drawbacks. In order to formulate a policy that reconciles the tension between beneficence and autonomy, I then follow a course of argument famously set forth by political philosophers Robert Wolff and Harry Frankfurt.

Wolff posits that individuals, insofar as they have the ability to choose, are responsible for the choices they make. The result, he states, is that individuals may not delegate these choices to a set of representatives, because such actions would, in essence, comprise of an unconditional obedience to others' commands. Frankfurt, however, counters by noting that there is nothing wrong with following others' edicts, as long as they remain within a certain set of limits we deem acceptable to ourselves.

The idea of willfully relinquishing a limited degree of autonomy that emerges from these arguments is central to the present paper. I argue that conditions which research has demonstrated responsive to placebo treatment should be treated in this fashion. In the form of a

renewable contract, patients may voluntarily allow physicians to prescribe placebos when they deem fit, while working within a pre-arranged, circumscribed framework. This agreement would resolve the contradiction between autonomy and beneficence that hampers many clinicians, and would allow for the selective use of deceptive practices. I conclude the paper by addressing a number of potential criticisms facing the idea of predetermined consent.

Pre-determined informed consent for deceptive placebo use in clinical practice

Until the 20th century, a significant proportion of medicine comprised of treatments with negligible pharmacological effects (Shapiro & Shapiro, 2000). While some, such as homeopathic cures, may have been inert, other therapies were downright dangerous (e.g., trepanation). Patients' improvement as a result, if not in spite of these cures, seems to have stemmed from the placebo effect—an improvement due to "psychobiological changes generated through the clinical encounter that are not attributable to the inherent chemical or physical properties of the intervention" (de Jong & Raz, 2011). At present, research has concluded that the placebo effect relies on an individual's expectancies of improvement; a conditioned response to treatment; characteristics of the therapeutic relationship; the attitudes and actions of the clinician; and the treatment context (Benedetti, 2009; de Jong & Raz, 2011).

In truth, physicians were frequently cognizant of the impressive degree to which their patients improved based on their beliefs alone, and often administered inert treatments to patients without their knowledge (Brody, 1982). Such deceptive practices persisted as long as physicians assumed a paternalistic attitude to their patients. To many, the "doctor knows best" approach, consisting of using expert medical judgment to heal a patient with no concern for their views and preferences, fit the idea of beneficence—a central tenet of medicine which comprises of an obligation to further others' interests by removing harms, and balancing the potential benefits of a medical action against its risks (Beauchamp, 2007).

Indeed, throughout the latter half of the 20th century clinicians frequently implemented treatments without the consent, let alone awareness, of those under their care (Collier & Haliburton, 2011). After numerous public scandals demonstrated the disconnect between patient

interests and the modus operandi of the medical establishment (Collier & Haliburton, 2011; Skloot, 2010), however, the concept of patient autonomy—the importance of respect for an individual's freedom and choices—came to the fore (Beauchamp, 2007).

In this present paper, I discuss the ethical tensions between beneficence and patient autonomy in the context of deceptive placebo use in the clinic. I then note the frameworks available to mitigate this strain, and mention their drawbacks. I then suggest another solution, in the form of pre-agreed informed consent, stemming from ideas developed in political science (Frankfurt, 1973; Wolff, 1970). Finally, I conclude by addressing a number of practical and theoretical challenges likely to emerge in response to this concept.

Ethics of deceptive placebo use in the clinic

The Council on Ethical and Judicial Affairs, responsible for developing the American Medical Association (AMA)'s stance on ethical issues, sets a somewhat limited position on placebos in the clinical setting (Bostick et al., 2008). The AMA's guidelines state that physicians may use placebos to aid in diagnosis or treatment only when a patient "…is informed of and agrees to its use… A physician should enlist the patient's cooperation by explaining that a better understanding of the medical condition could be achieved by evaluating the effects of different medications, including the placebo. The physician need neither identify the placebo nor seeks specific consent before its administration." As a result, we are left with a mismatched smorgasbord of disparate suggestions, and no concrete guidelines to use. Two particular problems accompany this definition.

First, the recommendations are thoroughly dangerous with regards to placebo use as diagnostic tool. Although the use of inert substances used to be commonplace when diagnosing

conditions such as epilepsy, neurologists have noticed that infusing patients with inert substances was liable to lead to seizures (a negative version of the placebo effect, deemed "nocebo effect"), and could not discriminate between true epilepsy and non-epileptic conditions (Bernat, 2011). The diagnostic use of placebo may, therefore, be dangerous to the patient.

Second, the verbal contortions on the topic of improving our understanding of the condition by evaluating various medications alongside a placebo, as suggested by the AMA, strike me as a somewhat half-baked compromise. Rather than using a straightforward clinical procedure, the obedient physician should befuddle the patient with talk of testing various non-specified substances. If anything, such a cloak-and-dagger approach to diagnosis would alarm the patient even more, and turn the practice of placebo-giving into an ordeal for the individual whom it is meant to benefit.

The problems with the AMA's guidelines appear to stem from its attempt to rectify two conflicting values: patient autonomy and beneficence. Not surprisingly, the present hodgepodge of suggestions suffices neither placebo advocates, nor its detractors.

While the general argument comes in several forms, scholars and physicians opposed to deceptive placebo use in the clinic typically state that the practice ignores the necessity for a patient's informed consent (Barnhill, 2011). In failing to receive consent, deceptive practices—including those rooted in beneficence—violate patient autonomy and impinge on both the quality and trust of the therapeutic relationship (Asai & Kadooka, 2012; Barnhill, 2011; Bostick et al., 2008).

Conversely, the most ardent defenders of deceptive placebo use believe that autonomy remains unaffected. Bennett Foddy suggests that administering a placebo, when no other treatment is available, does not constitute deception because it does not limit a patient's choice of

treatment—since no alternative exists, the placebo is the only course of action, and the patient would have been unable to autonomously choose another intervention (Foddy, 2009). Similarly, Foddy claims that the dispensation of placebos does not entail any coercive elements: since it is a suggestion, its use does not, strictly speaking, mean that the physician has forced a patient to consume something which affects them against their will (Foddy, 2009). Others, such as Kolber, simply state that autonomy remains inviolate because patients, if aware that they may derive a benefit by doing so, are likely to choose the placebo anyway (Kolber, 2007).

Both sides of the argument, however, seem excessively partisan. I find it unfathomable that, as some authors prefer, we completely abandon the use of placebos to help the ill (Asai & Kadooka, 2012). Foddy's arguments, too, set off distant moral alarms despite their logical tenor: while it may be a suggestion, it is nonetheless powerful enough to result in physiological effects, and undoubtedly has some coercive elements; meanwhile, the explanation that the placebo is the lone course of action fails when we consider that a patient may simply choose to seek a second opinion from another doctor, or omit treatment altogether. Kolber, while stating that his justification does not encroach on the concept of patient autonomy, is right insofar as he simply chooses to ignore its presence—there is a marked difference between independently choosing a course of action, and having it imposed on you because you *may* have chosen it (Barnhill, 2011).

Prospective solutions

Three solutions have emerged to mitigate the discord between autonomy and beneficence. The first, envisioned by Shaw, rests on the idea of Negatively Informed Consent (NIC): rather than explaining a proposed treatment to a patient, the physician states its intended effect, and asks the patient whether or not they desire more information (Kihlbom, 2008; Shaw,

2009). If the patient does not require it, the physician simply proceeds in implementing the treatment. The NIC procedure, in tandem with placebo use, allows the patient access a minimum of information, while autonomously deciding whether or not they require additional briefing.

The second ethical framework, designed by Mary Rawlinson, takes a more radical approach. Rawlinson states that illness detracts from an individual's autonomy; rather than violating autonomy, therefore, physicians *restore* it through treatment, be it deceptive or not (Rawlinson, 1985). In this scenario, beneficence and autonomy are spliced together; the conflict is resolved before it has a chance to arise.

The final method of reconciling autonomy and beneficence in clinical placebo use consists of examining just which treatment characteristics patients need to be informed of. Barnhill notes that patients typically desire only the most fundamental information when seeking treatment; if the benefits are likely and side-effects improbable, patients are unlikely to inquire about the specific mechanisms through which an intervention functions (Barnhill, 2011; O'Neill, 1984). While placebos may be inert, and we may be uncertain of their specific workings or chances of success, Barnhill suggests that such information is superfluous in many of the instances where they may be employed.

Each of these conceptions, however, is somewhat problematic. Rawlinson's conception of illness and autonomy is so radical that most physicians would be hesitant to adopt it. Barnhill and Shaw's proposals, while less surprising, are no less contentious: rather than quelling the dispute, they redefine the concepts of deception and consent. In essence, Barnhill states that notifying patients of the treatment's nature is unnecessary, and does not constitute deception; Shaw, on the other hand, decides to omit the "informed" aspect of consent, seeking instead a vague form of assent from patients.

A political perspective

Robert Wolff, a political scientist of some renown, published a well-known essay entitled "In Defense of Anarchism," in which he developed the idea that anarchism was an ethical necessity (Wolff, 1970). Wolff posits that insofar as individuals have the freedom to act, they have a moral responsibility to choose the right action. Specifically, he states that all autonomous people must use their own principles and judgments regarding which course of action to take; if they unconditionally follow a set of commands issued by someone else, autonomy is compromised. In fact, because any representative or majoritarian system of government is liable to take a course of action which differs from one's own personal choice, Wolff concludes that any position other than anarchism is morally unacceptable because it sacrifices one's autonomy (Wolff, 1970).

In response, the eminent political theorist Harry Frankfurt notes that Wolff's logic is flawed (Frankfurt, 1973). Frankfurt points out that Wolff, in essence, opposes unconditional obedience to authority. Thus, if we take autonomy to mean *solely* listening to one's own commands, any political stance but anarchism is impossible. If, however, we see autonomy as Wolff's writing suggests he himself does—requiring that we accept commands conditionally, and that we remain the arbiters of whether or not these conditions are met—a radical stance is unnecessary (Frankfurt, 1973).

This set of arguments holds key implications for the debate on deceptive placebo use. If we choose to see autonomy in a thoroughly rigid manner, it becomes difficult to support any form of deception in placebo use. If, however, we agree that we may remain autonomous while setting out the conditions under which we deem our autonomy to be compromised (i.e., the

actual, tempered version of autonomy that we, as social beings, see in our personal, political, and professional lives), a potential solution to the placebo dilemma emerges.

Predetermined informed consent

In order to reconcile the conflict between the values of autonomy and beneficence, I propose the idea of a pre-arranged consensus between physicians and their patients. This agreement, established at the outset of the therapeutic relationship, would outline the conditions under which a physician may employ placebos in a deceptive manner. The conditions themselves would be renewed periodically, with the physician obtaining renewed consent from the patient on a yearly basis.

Like all other therapies, clinicians would be limited in the use of placebos by the availability of scientific evidence. While hardened opponents of placebos may, at times, state that there is scant scientific support their employment (Asai & Kadooka, 2012; Hrobjartsson & Gotzsche, 2001), the academic community is, in large part, in agreeance regarding their efficacy in certain pathologies (Benedetti, 2009). Researchers have clearly demonstrated that conditions such as irritable bowel syndrome and depression are amenable to placebo treatment (Blease, 2011; Kaptchuk et al., 2008); in fact, in cases of mild to moderate depression, placebos match Prozac's effectiveness (Kirsch, 2010). Much as with any other therapy, the principal requirement for placebo use would be a solid pattern of replicable studies demonstrating their potency for a given condition.

This idea of a predetermined set of circumstances wherein clinicians would be allowed, by patients themselves, to engage in placebo use avoids the issues surrounding the previously listed solutions. Unlike Rawlinson's proposal, the current definitions of autonomy and illness

remain in the same conceptual space (Rawlinson, 1985). Moreover, this framework would ensure that the patients explicitly give consent for placebos to be used—unlike the propositions put forth by Shaw and Barnhill (Barnhill, 2011; Shaw, 2009).

Potential criticisms

While this is, to my knowledge, the first instance of a pre-arranged patient-doctor contract regarding placebo use in the academic literature, certain reactions against the general conception of using agreements to ensure informed consent have emerged.

Kolber, believes that advance consent is problematic for two reasons (Kolber, 2007). First, he states that even though a patient may give their consent to experience some manner of deception in October, they may still experience negative feelings when they are deceived several months after agreeing. Kolber does not cite any evidence regarding the likelihood of patients becoming offended or feeling wronged, so it is difficult to argue his point. Recent research, however, suggests that the patient acceptability of placebo is dependent on its effects (Kisaalita, Roditi, & Robinson, 2011). 103 web-survey respondents indicated that their approval of a physician who prescribed a placebo depended, in large part, on the placebo's efficacy. Keeping the problematic nature of assessing patient reaction through a hypothetical web-based vignette in mind, such findings nonetheless suggest that Kolber's conception of reactions to advanced consent may be contrary to actual reactions.

Had these negative physician evaluations existed, however, they would not have little bearing on patients' autonomy. Ornery reactions, no matter how unpleasant, frequently result from voluntary commitments. While I accept the responsibility that accompanies helping a friend move furniture, I may lament my acceptance throughout the act of physical exertion itself; that is

to say, while I frequently agree to undertake certain tasks, the development of negative feelings accompanying them is not only acceptable, but wholly expected. My autonomy remains intact: I am fully aware of my impending discomfort, and have made a considered, rational choice to experience it when going out of my way. By the same token, individuals who proceed to authorize their clinician to employ placebos willfully relinquish the requirement for complete awareness in advance of the fact, keeping their well-being in mind above all other factors. They autonomously agree to the idea of deception for personal benefit, and, one would think, would be satisfied as long as the placebo works.

Kolber's second objection is formulated thus: if patients sign an advance waiver regarding deceptive placebo use, they may lose the placebo effect that boosts the efficacy of other therapies (Kolber, 2007). Specifically, Kolber suggests that being informed that placebo administration may occur would lead individuals to be suspicious of all medications, minimizing the therapeutic benefits which accompany non-placebo interventions. Foddy, a strong supporter of deceptive placebos in clinical practice, echoes this concern (Foddy, 2011). If we strive for beneficence in practice, and forgoing deception leads to a decrease in the placebo's effect, must not physicians ensure to employ deception in order to maximize the patient's benefit?

Researchers largely agree that expectancies—the beliefs that something will occur as a result of a particular action or occurrence—play an important role in the placebo effect (Benedetti, 2009). Numerous studies have suggested that manipulating participants' expectancies of placebo efficaciousness leads to a decrease in the placebo effect: placebo morphine has a greater effect than placebo aspirin (Evans, 1974); larger placebo pills appear as more effective than smaller ones (Kirsch, 1997b); and injections have greater placebo effect than pills (Chaput de Saintonge & Herxheimer, 1994). Nevertheless, evidence demonstrating that changes in

expectancies modulate the placebo effect does not equate with support for the belief that advanced consent for deceptive placebo use decreases its efficacy in some meaningful way.

First, whether or not notifying individuals of potential placebo use *in the future* affects placebo response remains unclear (Miller, Wendler, & Swartzman, 2005). In one study, two groups of psychology students learned that they would experience a painful electric shock throughout the course of an experiment; researchers notified one group that deception was sometimes used in psychological experiments, while the second group received no additional instructions (Holmes & Bennett, 1974). While no shocks ensued, the two groups demonstrated no difference in signs of anxiety and arousal, suggesting that being forewarned of potential deception does not necessarily change expectancies. Similarly, I would assume that being notified of potential deceptive placebo use would not result in significant differences in placebo effect— the lack of certainty in this study, just like that in idea of pre-arranged informed consent, may be an important mitigating factor in expectancy manipulation.

Second, recent research investigating the use of open-label placebos suggests that patients may derive therapeutic benefits from placebos without the use of deception (Kaptchuk et al., 2010). IBS sufferers who received placebos alongside the notice that they were consuming "placebo pills made of an inert substance, like sugar pills, that have been shown in clinical studies to produce significant improvement in IBS symptoms through mind-body self-healing processes" fared better than IBS patients who received the same quality of care with no placebo intervention. While these results await thorough replication, such findings, at the very least, suggest that deception is not a necessary aspect of placebo administration. Notably, predetermining consent for placebo use does not require such extensive openness in protocol. Individuals would agree to the terms of use at the outset of their therapeutic relationship with

their physician, and have no certainty of when, if ever, they will be treated with a placebo. Additionally, the effects of such uncertainty coupled with the time-lag accompanying treatment would likely lead to the patient's diminished focus on placebo use, counteracting any potential change of expectancy which might result from the original consent. Of course, the dearth of available experimental data makes drawing any but the most general of conclusions difficult; nevertheless, sufficient evidence is available to cast doubt on the idea that a predetermined form of consent counteracts the placebo effect.

Conclusion

The deceptive of use placebos in clinical settings is a controversial issue, pitting the values of physicians' beneficence against patients' autonomy. While staunch opponents of deception claim that any manner of placebo use stands in violation of autonomy due to its circumvention of informed consent, supporters assert that placebo use does not violate autonomy. Although the AMA has attempted to reconcile the strain between these camps, their positions appear too radical to appease by compromise; numerous scholarly frameworks for rectifying this tension, meanwhile, have ignored the importance of informed consent.

In this paper, I have suggested that physicians seek predetermined informed consent from their patients in order to make use of deceptive placebos, where such use is scientifically justified. Furthermore, I have addressed the most probable criticisms that this proposal may face. In the realm of placebos, it seems, the bliss of health need not stem from ignorance.

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