A reappraisal of the role of 'mindbody' factors in chronic urticaria

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ABSTRACT

Chronic spontaneous urticaria (CSU) is a very common skin condition that causes considerable suffering and is often poorly responsive to drug treatment regimens. Most clinicians accept that multiple factors play a role in the aetiology of CSU, but there is a widespread reluctance to accept a significant role for 'mindbody' factors, despite a large number of clinical reports and studies over many decades suggesting their relevance. This reluctance has multiple origins. A primary influence is the flawed dualistic model of mind and body relatedness underpinning much of modern medical care. In this view, if a pathophysiological mechanism can be discerned, then 'mind' factors can be largely ignored. Recent evidence demonstrating intimate structural and functional relations between peripheral nerves and mast cells, and local skin secretion of mast cell-influencing neuropeptides by nerves, provides an argument for discarding old 'organic' and dualistic conceptualisations of CSU. A sound, integrative, multifactorial approach requires a unitive 'mindbody' model in which physical and subjective dimensions of personhood are seen as coexisting and equally deserving of exploration and management. Another influence is the tendency for 'psychosomatic' research studies in CSU to focus on patient experience using broad group-based diagnostic categories, such as anxiety and depressive disorders, and generic measures of stress. Two case examples are given, illustrating that CSU arises in relation to highly individual and relevant 'stories', which would not usually be picked up by these generic measures. It is suggested that an appropriate 'mindbody' management programme leading to good clinical outcomes for CSU is dependent on clinicians discerning unique patient 'stories'. Finally, a lack of formal studies comparing drug and 'mindbody' treatment outcomes will continue to negatively influence the adoption of 'mindbody' approaches in CSU. There is an urgent need for properly structured comparative studies, and the essential elements of a suitable 'mindbody' approach appropriate to such research are briefly outlined.

INTRODUCTION

For 21st century allergists and dermatologists, the aetiology of many cases of the common condition chronic spontaneous urticaria (CSU)[1] remains as much a puzzle as it was for the 19th century Austrian authority, Ferdinand Hebra, who wrote: 'We are for the most part ignorant of the causes of chronic urticaria'.[2] The thesis here is that a significant proportion of chronic urticaria is perceived as 'idiopathic' in the 21st century because psychological, 'mindbody', or 'story' factors *are* important in the aetiology of the condition, yet remain largely *invisible* to clinicians managing the condition, even though 'casuistic material purporting to show the effect of psychological factors on urticaria exists in abundance'.[3]

A brief historical comment allows some understanding as to why clinicians have waxed hot and cold on the psychological aspects of urticaria. The first half of the 20th century saw a roughly concurrent emergence of psychoanalysis, with its discoveries of human psychological defence mechanisms, and of allergy as a clinical specialty based on a rapidly growing understanding of antigens, antibodies, antibody specificity and antigen/antibody reactions. Thus, in the 1940s and 50s, there was significant interest in the relations between psychodynamics and allergic processes,[4] some reports[5] providing extremely detailed analyses of complex emotional scenarios leading to urticaria. As the century progressed, a massive growth in immunological knowledge, the increasing dominance of the biomedical model of disease, and disenchantment with some aspects of psychoanalysis all combined to push 'mindbody' conceptualisations of urticaria to the margins of orthodox allergy practice.

> 'Mindbody' factors in chronic urticaria have been reported by clinicians for decades.

Nevertheless, references to psychological aspects of urticaria have kept surfacing in an extensive medical literature. In 1940, Stokes claimed psychological factors were important in 79% of urticaria.[6] Graham *et al*[7] observed in 30 closely studied individuals with urtication that there were strong correlations between feelings/attitudes, vascular skin responses, and urticaria. Significantly, Shoemaker[8] found that urticaria often responded to psychotherapy, and concluded it was simplistic to search for a generic emotional theme, stating 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'. In my view, little has changed to alter that judgement,[9 10] despite various attempts to reduce the understanding of urticaria to its relationships with feelings on the anger spectrum,[11 12] to diagnoses of anxiety and depression,[13–15] to the diagnosis of alexithymia,[16 17] and to specific pathological personality traits.[18]

The findings of studies bearing on 'mindbody' factors in CSU will be summarised alongside and within a discussion of the dualist assumptions underpinning medical practice and the 'essentialist' methods of research studies which tend to steer

researchers away from the specific life experiences ('stories') peculiar to each patient. A picture emerges in which many clinicians over many decades have recognised the presence of 'mindbody' factors in CSU, but few feel much justification for deploying a 'mindbody' approach in treatment, or, indeed, for research studies comparing drug and 'mindbody' treatment outcomes. Finally, a framework is suggested for making progress in establishing a clinically useful practice that includes 'mind-body' approaches in partnership with biomedical treatments.

URTICARIA, A MULTIFACTORIAL DISORDER

Stokes[6] asserted the multifactorial nature of urticaria, stating that psychological factors must be conceived of as 'acting in a complex of hereditary, physiologic, bacteriologic, immunologic, and other pathogenic and protective-reactive agencies'. Most modern allergists would agree that chronic urticaria is often triggered by multiple factors,[19–21] including food chemicals, aspirin and non-steroidal inflammatory drugs, febrile illnesses, and autoimmune factors, often acting in unison. In two 2009 urticaria guideline publications,[1 19] psychological factors are mentioned in passing, and it is stated 'that effective management process could take into account, at least in some patients, psychological factors'.

MEDICAL DUALISM AND ORGANICITY

Nevertheless, the possibility that psychological factors may be a very important influence in CSU seems unpalatable to many clinicians. The problem seems to be, in part, the prevalence of a dualistic *either/or* approach to disease causation, in which illnesses are seen as entirely physical ('organic') or entirely psychosomatic ('functional'). That is, if a pathophysiological mechanism for the urticaria can be discerned then 'mindbody' factors can be dismissed. In the psychoanalytical/allergy 'dance' period of the 1930s–40s, the tensions implicit in this dualistic approach to disease were clearly seen. Weiss,[4] referring specifically to allergic disorders, cautioned: 'Psychosomatic medicine does not mean to study the soma less; it only means to study the psyche more. When a person gets sick, he is sick all over—*the mind and the body are one*—he gets sick for a variety of reasons, physical and psychic' (italics added).

> Dualistic models of personhood limit clinical capacity to think of body AND mind together.

Asserting a psychological causation does not imply that there should be no measurable physical or 'organic' findings. In fact, modern psychoneuroimmunological research reveals numerous ways in which nervous system/immune system interactions may lead to mast cell activation and CSU.[22 23] The remarkable bidirectional relationships between the skin and the central nervous system have been well summarised elsewhere.[22 24–26] Both arise from the same embryonic ectoderm, and they share various hormones, neurotransmitters and receptors. Panconesi and Hautmann[25] emphasise the innervation of the skin by sensory nerves, post-ganglionic cholinergic parasympathetic nerves, and adrenergic and cholinergic sympathetic nerves, and that the sensory nerves also function in an efferent 'neurosecretory' capacity. Signal pathways include local nociceptors *to* afferent C fibres *to* dorsal root ganglia and dorsal horn *to* ascending pathways *to* thalamus *to* higher cortical centres (with cognition/perception input) *back to* spinal cord *to* autonomic responses in the skin. There is little doubt now that 'stress' can disturb peripheral conditions via activation of autonomic nervous system or hypothalamic–pituitary–adrenal (HPA) pathways,[27] or via richly complex interactions between mast cells and local skin nerve fibres.[28]

> Finding measurable pathophysiological changes does not rule out 'mindbody' factors.

These central nervous system–skin interactions involve numerous hormones, cytokines produced by immune and other local skin cells, and molecules such as substance P secreted by local nerves. Hemokinin, calcitonin gene-related peptide, β-endorphin, endothelin, hormones of the HPA axis, kallikreins, proteases, nerve growth factor, neuropeptide Y, pituitary adenylate cyclase-activating polypeptide, and substance P all influence mast cells and are released in a stress response.[23] Substance P is secreted by sensory nerve fibres, causes mast cell histamine release, and is 100 times more potent than histamine in causing wheal/flare, and is a potent cause of pruritis.[25] The neurotrophin, nerve growth factor, is a particularly potent mediator of inflammation prompted by stress [29–31] and has mast cell-releasing effects.[22] Thus, it is clear that there are a host of potential molecules with capacity for influencing mast cell-mediated proinflammatory behaviour. These findings have implications in allergy practice well beyond a focus upon CSU. For instance, Kimata[32] has shown that stress (in the form of sustained video game playing) in patients with atopic dermatitis significantly increases allergen wheal size, increases the levels of substance P and nerve growth factor, and increases the in vitro production of allergen-specific IgE.

Thus, it appears increasingly naive to assume that, because there are definite indications of pathophysiology (visible welts, or measurable changes in cell-influencing mediators), 'mind-body' factors need not be considered. It is clear that the neuroimmune and neuroendocrine mechanisms governing mast cell secretion, degranulation and pruritis are extremely complex, and this is a likely explanation for why simple antihistamine treatment can be quite ineffective in CSU. It could even be that addressing important psychological factors may be a more efficient method of treatment than finding multiple drugs capable of adequately moderating or blocking complex biochemical mechanisms, and this is my clinical experience.

But clinicians do commonly disregard the role of psychological factors if there are seen to be other non-psychological factors. For instance, in 60% of patients with active CSU, a circulating 'histamine-releasing factor' has been identified, and numerous humoral candidates for such a role have already been mentioned. Half of these patients have evidence of autoantibodies to the α subunit of the high-affinity IgE receptor and/or IgE itself.[20 33–35] Findings such as this seem to trigger the dualistic *either/or* thinking referred to above. For example, one author's response: 'Thus a fraction of patients with chronic urticaria formerly often associated with psychosomatic illness suffer *in fact* from an autoimmune disorder'(italics added).[36] The assumption is made that, because certain markers of autoimmunity can be identified or measured, then clinicians must turn away from a 'mindbody' modelling of CSU, or for that matter any other illness. For clinicians with this 'hard' dualistic attitude, the presence of the 'autoimmune' precludes psychogenesis. It thus appears that the biomedical model underlying much of the modern approach to disease makes it difficult for clinicians to imagine that a florid condition such as chronic urticaria, associated with obvious mast cell mediator release and effects, and clearly visible to the evidence-oriented eye, can really have its origin (partly or solely) in psychological factors. Amazingly, a review article on psychodermatology[37] does not even mention

CSU, despite holding a strong psychological orientation to skin conditions, and even subscribing to the view that a skin symptom can be seen as a 'coded message'.[38]

Despite the 'hard' dualism seen in many quarters, and a correlating widespread reluctance to look at psychological factors, there is, ironically, a ready acceptance of a brain-to-body causal connection—for example, in cholinergic urticaria where the lesions can be replicated with methacholine injections into the skin, and in the rare adrenergic urticaria where the lesions can be replicated with injections of noradrenaline and blocked with β blockers.[39 40] Thus, in certain restricted circumstances, there is a surprising, not very well rationalised, acceptance of psychoneurological effects upon mast cells causing urticaria.

The point is that a *non-dualistic* construction of persons, illness and disease would expect the coexistence of psychological factors and measureable pathophysiological processes, and therefore, within a non-dualist construction, none of the recent autoimmune or other 'physical' findings rule out a role for psychological factors.

A non-dualistic view of persons imagines physical mechanisms and 'mindbody' factors as different dimensions of one integrated process.

STUDIES EXPLORING 'MINDBODY' FACTORS

Assuming for the moment that psychoneuroimmunological modelling of CSU has some plausibility, what is known at the clinical level of the 'mindbody' factors that may lead to CSU? There are numerous reviews revealing what clinicians and researchers have focused upon and observed.[2 20 21 41 42] The essential findings will now be summarised.

In 1948 the American College of Allergists published a small official monograph entitled 'Psychodynamics and the allergic patient'.[4] Starting from Hippocrates, Abrahamson provides fascinating historical insights into 'psychosomatic' factors in allergic conditions. Most of the clinical stories echo those of other 'mindbody' clinicians,[9 10 43–48] and many show a remarkable entanglement of the patients' highly specific life meanings with the onset and trajectory of various illnesses, to the point one could say the illness is symbolic, or a 'somatic metaphor'.[10 45] For example, Abramson provides a fascinating account of the development of cold urticaria after a patient nearly drowns. The patient wanted to drown, because of mental conflicts involving guilt she felt related to friends dying while serving in the armed forces. But Koblenzer[41] has pointed out that the psychosomaticists of the 1940s and 50s were inclined to look for specific emotional themes, or 'specific unconscious conflictual or personality constellations,' *typical* of each illness. This desire to find clean, generic, core psychodynamic and affective themes characterising individual physical disease diagnoses is highly reductionist and, as has been emphasised elsewhere,[9 10] generally too crude to be of real benefit to an individual patient, firstly, because engagement with patients is usually destroyed by reducing their uniqueness to a generic theme and, secondly, because the themes of individuals are too richly nuanced to be usefully reduced to broad categories.

Perhaps the simplest of the reductive generic approaches is seen in the use of the 'stress' model. It is clear that, in animals, 'stress' will cause mast cell degranulation.[49] In humans, investigators have typically focused upon generic 'life events' questionnaires, based on research into what the community-at-large would acknowledge to be stressors. This 'essentialising' approach,[50] which renders invisible those micro-events peculiar to the individual, putting them outside the screening capacity of non-specific questionnaires, does not produce convincing evidence. For example, one study,[51] applying a 'Presumptive Stressful Life Events (PSLE) scale' to patients with urticaria, showed that only 16% of patients suffered stressful life events in the year before onset. However, a dermatology clinic study,[52] while adopting an essentialising approach, but using multiple questionnaires and accessing a broad range of patient function and experience parameters, showed that patients with urticaria (when compared with patients with tinea pedis) showed significantly more *prior* stressful life events, psychosomatic symptoms, insomnia and irregularity of daily life, and significantly less social support, resilience and coping capacity.

Exploring highly individual 'story' data should be the focus of 'mindbody' assessment.

An alternative to 'essentialisation' is a rigorous individual patient-centredness or individual 'story' approach,[9 10 43–45] looking for those unique things in the patient's life that he/she *is* experiencing adversely, whether other people deem them worthy of the 'stress' category or not. Two examples illustrate this point.

A 66-year-old woman, a retired librarian, single, with many interests and hobbies, and apparently enjoying reasonable psychological equilibrium presented with a 6-month history of very severe and constant urticaria and angio-oedema, at times affecting the larynx, and unresponsive to a wide range of anti-allergic treatments including steroids. At presentation, there was little evidence of any biological or psychological factors, and over the next 6 months attempts to control the condition with medication continued to be unsuccessful. At the end of this period, careful in-depth psychological enquiry revealed that, just before the onset, her mother aged 89 had been taken into hospital with a minor 'stroke', had recovered, but on returning home was refusing to wear her hearing aids. The patient had lived with her mother all her life, had a life-long pattern of non-assertiveness and could not 'tell her' to wear them, was in effect losing her mother, and was getting frustrated. She was advised to persuade her mother to wear the hearing aid, and within 3 h the urticaria had gone. Some weeks later it returned, and the patient presented again in the clinic. She was asked about the hearing aids. Curiously, the patient had 'forgotten' about this, and the mother had ceased using them. The hearing aids were reinstated permanently, and the urticaria remitted permanently.[43]

A 75-year-old man presented for a second opinion regarding severe unremitting urticaria/angio-oedema for 5 years. He had failed to respond to high-dose antihistamines (H1 and H2), colchicine, hydroxychloroquine, a salicylate-free diet, and intravenous immunoglobulin. Prednisone was minimally effective, but he used it as 'rescue' medication. A 'mindbody' psychotherapy approach[9] revealed that the condition started during a year when he was organising a carnival event and felt very 'inadequate'. There was also an ongoing frustration with his marriage. Addressing the latter aspect led to an early reduction of symptoms. But there were also very specific problem situations. Toileting led to an unusual and severe pruritis and urticaria restricted to the pelvic girdle area. Showers and bathing had ceased because of heat and water relatedness (there was no evidence of aquagenic or cold urticaria). The toilet symptoms ultimately seemed to relate to 'absolute rage' originating in being held over the 'pot' from 6 weeks of age, a pattern his mother tried to enforce again with the grandchildren. Once the connections were made, the patient was able to approach toileting differently and without symptoms. The heat and water

scenario seemed to be related to risk management and control, and addressing these issues led to a further sharp reduction in symptoms. By the 6th session he was much better and starting to reduce his drugs. At 12 sessions, he reported being '95% better' with only an 'occasional itch' and taking antihistamines infrequently. The improvement is sustained 6 months later, at the time of writing.

Both cases had been very difficult to manage with conventional drug treatments. In the first, making the association between frustration and the urticaria was enough to mobilise improvement. In the second, there seemed to be more entrenched and historical 'threads' that needed addressing. These kinds of 'stressor', highly specific to an individual, would not have been detected by a questionnaire searching for generic stressors. But despite the limitations of *generic* stress modelling of CSU, it does generally support a role for stress. Rees[53] reported on 51% of 100 patients with CSU experiencing antecedent stressful situations compared with 8% of surgical controls, although Fava *et al*[54] claim that 90% are exposed to stressful situations before onset. In one study,[55] 77% of patients reported tension and fatigue as major factors, and in another[56] patients cited stress (36%) as the single largest factor aggravating urticaria, more than heat (23%) or analgesic drugs (8%). Czubalski and Rudzki[12] claim that 'frustrating situations' are associated with 80% of dermographism and 75% of adrenergic urticaria cases. Kimyai-Asadi and Usman[57] refer to 'isolated case reports' of urticaria occurring in the context of events such as earthquakes and dental procedures.

Shifting from an emphasis upon stress, there have been many reports that accord a role in CSU to negative affect and psychodynamic themes. Individual patient case studies[9 10 12 21 43] highlight the role of anger spectrum affects (rage, anger, resentment, frustration, irritation). Such affects may be suppressed or repressed,[58] and unrecognised by the patient, and indeed the clinician.[43] In a search for 'essential' specific psychodynamic processes and meanings, Wittkower and Russell[3] studied 35 unselected patients, and two-thirds 'stated spontaneously that they missed parental and especially maternal affection as children'.[25] The authors refer to 'repressed aggressiveness' somatised to the skin. Panconesi and Hautmann[25] go further and allude to the possible symbolic aspects of urticaria. The sudden quickness of the lesions, the redness and swelling, the pruritis, irritation and burning, and the (at times) extreme scratching all (in the symbolic and psychodynamic view) suggestively parallel the human experience of affect on the anger spectrum (anger, rage, irritation, frustration, resentment). This is consistent with modern concepts of embodiment in which subjective experience is deeply rooted in the body and physicality.[59–63] My experience suggests that many patients with urticaria represent anger spectrum affects in the body. In line with this, Daniels[64] refers to a study[65] of wheals induced 'on the arm of a subject asked to imagine being struck on the arm by members of his family toward whom he harboured resentment'.

THE NEED FOR 'MINDBODY' THERAPY STUDIES

Despite this long history of attention to the 'mindbody' factors in CSU, there has been no systematic trial comparing a suitable psychological therapy with orthodox biomedical therapies. This probably reflects the emphases of the biomedical model and its dualistic assumptions. Daniels[64] presents a case of chronic headache and chronic urticaria treated very efficiently with sophisticated behavioural techniques addressing very specific interpersonal situations and the downregulation of tension, anxiety and anger responses. Hypnosis has a long history in the treatment of skin disorders,[66 67] and a study using a very basic relaxation-plus-hypnosis approach, which did not address any interpersonal dynamics possibly associated with symptoms, showed reduction in pruritus but not urtication.[66] Urticaria associated with post-traumatic stress disorder appears to respond to Eye Movement Desensitisation and Reprocessing techniques.[68] Hashiro's case study[69] focuses upon affect ventilation, psychological support, and action to remove key stressors. Assuming the importance of 'mindbody' factors, and the multifactorial nature of CSU, Keegan[21] outlines very succinctly a patient-centred approach that takes full cognisance of the physical and psychological factors, and tailors the treatment response to each individual. But this, like others,[9 10 43] is based on cumulative clinical experience, rather than systematic trials of psychotherapy compared with conventional biomedical approaches. In literature reviews of CSU, stress reduction is sometimes recommended, mostly in passing,[20] but all tend to give priority to the biological aspects, and some are merely dismissive of the 'mindbody' factors.[42]

CSU is a multifactorial and heterogeneous disorder, and one could reasonably expect there to be diversity from case to case in terms of the relative contributions of physical and non-physical factors. This diversity will in turn influence the likelihood of spontaneous recovery. CSU tends to remit over time. Kozel *et al*[56] showed that 47.4% of patients with CSU were free of symptoms after 1 year. Toubi *et al*[70] claim that, after exclusion of patients with chronic infection, physical urticaria, specific food allergy skin test positivity, and food chemical hypersensitivity (on the basis of response to a food chemical-free diet), the natural history of CSU is as follows: at 6 months 94% are still active, at 12 months, 75%, at 24 months, 52%, at 36 months, 43%, and at 60 months, 14%. In those with angio-oedema, positive autologous skin tests, or antithyroid antibodies, the CSU tends to last longer, and in those with autologous skin test positivity, it tends to be more severe. Autologous skin tests were positive in 28% of patients in their study. Again, CSU is a heterogeneous disorder and the influence of any factor including the psychological will vary from case to case.

CONCLUSIONS

CSU is a common disorder that causes a great deal of suffering and often responds poorly to antihistamine drugs, necessitating recourse to a variety of drugs, some of which have significant side effects and may be ineffective. There is clinical and research evidence that has appeared over many decades that psychological factors are important. Once one accepts a unitary ('mindbody') rather than a dualistic (mind *or* body) view of urticaria, there is no reason why considering 'mindbody' aspects should be ruled out in any case of CSU, whether there are measureable pathophysiological findings or not. What needs to be determined formally is how often 'mindbody' approaches are useful, how effective they are compared with other therapies, what are the healthcare economic implications of 'mindbody' approaches to this condition, and to what extent this kind of care may make certain types of pharmacological treatment and dietary restrictions redundant.

Main messages

Formal outcome studies comparing drug and 'mindbody' treatments are needed. The 'mindbody' approach used must be non-dualistic, and tailored to the individual patient 'story' and need rather than to a clinician's preferred methodology.

There has been no systematic outcome study comparing an orthodox drug treatment approach with a suitable 'mindbody' approach. The essential elements of such an approach, suitable for chronic urticaria, have been detailed elsewhere,[9 10 44 45] but, in short, are: a determined non-dualistic *both/and* mind and body integration; an eclecticism that accommodates a range of psychological modalities including psychodynamic, cognitive/behavioural, stress-reduction, and affective expression emphases; proper attention to physical as well as psychological triggers; and clinicians who are confident and skilled in holding mind and body dimensions of personhood together in the same clinical time/space.

MULTIPLE CHOICE QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AFTER THE REFERENCES)

1. The cause of chronic urticaria is most commonly:
   A. food chemicals such as salicylates
   B. anti-IgE autoantibodies
   C. multifactorial including emotional factors
   D. caused by food allergy
   E. revealed by careful skin testing
2. The emotional factors in chronic urticaria:
   A. are neglected because of dualistic assumptions underpinning biomedical models
   B. are always rooted in the anger spectrum
   C. cannot be accessed by physicians
   D. have been recognised since the 19th century
3. The release of mediators from skin mast cells causing urticaria:
   A. always involves IgE molecules
   B. may be mediated via local skin nerve fibres
   C. may involve substance P, neuropeptide Y, and nerve growth factor
   D. can be caused by skin pressure
   E. always requires an allergen whatever other factors are involved
4. The drug treatment of chronic urticaria:
   A. is nearly always successful
   B. is often difficult
   C. often results in polypharmaceutical approaches
   D. may be combined successfully with psychological approaches
5. Psychological approaches to chronic urticaria:
   A. should be deployed after biomedical approaches have failed
   B. should be deployed in concert with biomedical approaches
   C. should only be enacted by a trained psychologist or psychotherapist
   D. require a clinician working from a non-dualistic illness model

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ANSWERS

1. (A) F; (B) F; (C) T; (D) F; (E) F
2. (A) T; (B) F; (C) F; (D) T
3. (A) F; (B) T; (C) T; (D) T; (E) F
4. (A) F; (B) T; (C) T; (D) T
5. (A) F; (B) T; (C) F; (D) T

A reappraisal of the role of 'mindbody' factors in chronic urticaria

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