

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <https://orca.cardiff.ac.uk/id/eprint/126273/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Ingram, J.R. and Ahluwalia, A. 2021. The pharmacology of itch. *British Journal of Dermatology* 184 (1) , e1-e2. 10.1111/bjd.18525

Publishers page: <http://dx.doi.org/10.1111/bjd.18525>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



Virtual issue - Itch

Editorial

The pharmacology of itch

Pruritus, commonly known as itch, has a substantial impact on quality of life in skin disease. Irritation of one of the largest organs of the body does not just directly impact upon the organ itself but underlies a plethora of indirect consequences for the patient that goes way beyond the desire to scratch. The psychological issues associated with chronic pruritus combine with disfigurement from scratching and sleep disturbance to produce mental health problems in many cases. While itch may be a consequence of cutaneous inflammation, symptom improvement by modulation of pruritus represents an important pharmacological target. There has been a lot of activity in the field recently, at both pre-clinical and clinical ends of the spectrum, providing a compelling case for a joint virtual issue between the BJP and BJD with a focus on novel therapeutics for pruritus. As the editors of the two journals we have each picked seven recent articles to share with our combined audiences.

Readers of BJP may not be aware that the BJD has a focus on particular core methodologies which determine the main sections of the journal: translational, trials, outcomes and qualitative research, epidemiology, and evidence-based dermatology. Similarly, BJD readers may not be aware that BJP is often the journal of choice for those researchers interrogating the mechanisms of pruritis and the testing of novel entities in appropriate *in vitro* and *in vivo* experimental models.

Considering translational research first, our virtual issue contains a review of Substance P and neurokinin 1 receptor as targets for the treatment of chronic pruritus.¹ Both entities are over-expressed in multiple chronic pruritic conditions, providing a rationale for translational therapeutic applications. The review covers several recent phase 2 clinical trials of neurokinin 1 receptor antagonists demonstrating potential clinical benefit. In addition, we include two original articles providing greater depth into our understanding of the mechanisms involved in activation of the sensory neurones containing these neuropeptides. We share evidence implicating both TMEM16A and reactive nitrogen species in activating TRPV1 and TRPA1 channels localised to nerve endings^{a,b}, thus identifying potential new avenues for limiting the itch sensation.

BJP has long been a journal home to developments in histamine and histamine receptor pharmacology. Accordingly in this issue we share the most recent updates on the role and targeting of histamine in itch and associated pain^c and recent progress in application of molecules targeting the H₄ receptor particularly^d. The journal is also home to some of the best pharmacology in purified natural products, an area with an explosion of interest in the recent decade. This explosion is exemplified by a recent article demonstrating the potential of Salvinorin A analogues preventing mast cell degranulation, and in this way potentially break the continuous cycle created by physical disruption of mast cells of itch-relief-itch^e.

BJP also has a long history in publishing research emanating from the prostaglandin field, being a title that has published some of the most highly cited papers in the field from the Nobel prize winning pharmacologist Sir John Vane; the 20 year anniversary of which was recently celebrated in a

separate themed issue in the journal^f. In this Virtual Issue we also include some exciting evidence identifying further utility for the somewhat maligned COX-2 inhibitors in modifying TRPV3 activity^g.

Oral Janus kinase (JAK)/spleen tyrosine kinase (SYK) inhibitors are one of the new set of small molecules that are under development for dermatological applications, including the pruritus associated with atopic dermatitis (AD). In a phase 1B randomised controlled trial investigating ASN002, an oral JAK/SYK inhibitor for moderate to severe AD, a 50 percent reduction in Eczema Area and Severity Index (EASI 50) was reached by a significantly higher proportion of patients who received higher doses of ASN002 compared to placebo.²

The BJD has established a strong pedigree in publishing outcomes research, which usually requires a qualitative aspect in the form of patient interviews to demonstrate content validity. Yosipovitch and colleagues combined patient interviews with trial data to establish that peak pruritus numerical rating scale is a reliable, sensitive and valid scale for assessing worst itch intensity in adults with moderate-to-severe AD.³

As mentioned in the introductory paragraph, one important potential consequence of chronic pruritus is a detrimental effect on mental health. Silverberg and colleagues performed a cross-sectional, population-based study of 2893 U.S. adults with AD and found significantly increased risks of anxiety and depression, using Hospital Anxiety and Depression Scale (HADS) scores, compared to those without AD.⁴ Some of the individuals with elevated HADS scores had not received a formal diagnosis, emphasizing the need for vigilance in this patient group.

The BJD champions evidence-based dermatology. A review article included in this virtual issue considers the problem of severe, treatment resistant pruritus associated with primary biliary cholangitis (PBC) in which destruction of liver bile ducts leads to intrahepatic cholestasis.⁵ Our understanding of pathophysiology is summarised by the review, including specific receptors such as G-protein-coupled bile acid receptor, Gpbar1 (TGR5) and the nuclear transcription factor farnesoid X receptor (FXR). Phototherapy can have some benefit and Hussain and co-authors employed a focused search strategy to propose testable hypotheses for the mechanism of action of phototherapy through modulation of these signalling pathways.

Explanatory randomised controlled trials generally have tight inclusion and exclusion criteria and their results may not always be generalizable to the wider patient population. So it is important to have real-world data to fill the gap. A study of 95 adult patients who received dupilumab for AD in the Netherlands in a non-trial setting found that results were in keeping with the phase III trial data for clinically relevant improvement of both physician-reported and patient-reported severity scores.⁶

As part of the BJD portion of this issue the BJD editor has included one additional 'editor's choice' article. As dermatologists we may take for granted use of newer antihistamines that have a lower tendency to cause drowsiness than first generation antihistamines (FGA). A cross-sectional observational study from the U.S. investigated antihistamine prescriptions following 15,000 dermatology consultations and 66,000 primary care appointments.⁷ The study found that FGA prescribing rates were 2-fold higher in primary care than secondary care when comparing matched cohorts. In addition, there was no reduction in prescribing rates in older adults, despite FGA being classified as "potentially inappropriate" in this population.

In sum, there has been considerable interest in the field of pruritis, not only in terms of direct treatment to attenuate the sensation and its physical consequences but also in terms of dealing with the sometime devastating effects upon mental health. This virtual issue bringing the BJP and BJD together shines a spotlight upon the most recent advances in the field in both journals.

Word count = 682

J.R. Ingram

Division of Infection & Immunity, Cardiff University, Cardiff, U.K.

A. Ahluwalia

William Harvey Research Institute, Barts & The London School of Medicine & Dentistry, Queen Mary University of London, UK

Correspondence: John R. Ingram and Amrita Ahluwalia

IngramJR@cardiff.ac.uk, <http://orcid.org/0000-0002-5257-1142>

a.ahluwalia@qmul.ac.uk, <https://orcid.org/0000-0001-7626-6399>

References

- 1) Ständer S, Yosipovitch G. Substance P and neurokinin 1 receptor are new targets for the treatment of chronic pruritus. *Br J Dermatol* 2019. doi: 10.1111/bjd.18025. [Epub ahead of print]
 - a) Liu, Shenbin; Feng, Jing; Luo, Jialie; Yang, Pu; Brett, Thomas J.; Hu, Hongzhen. TRPA1 activation leads to neurogenic vasodilatation: involvement of reactive oxygen nitrogen species in addition to CGRP and NO. *BJP*
 - b) Aubdool, Aisah A.; Kodji, Xenia; Abdul-Kader, Nayaab; Heads, Richard; Fernandes, Elizabeth S.; Bevan, Stuart; Brain, Susan D. Eact, a small molecule activator of TMEM16A, activates TRPV1 and elicits pain- and itch-related behaviours. *BJP*
 - c) Obara et al. Histamine, histamine receptors, and neuropathic pain relief. *BJP*
 - d) Schaper-Gerhardt, Katrin; Rossbach, Kristine; Nikolouli, Eirini; Werfel, Thomas; Gutzmer, Ralf; Mommert, Susanne. The role of the histamine H4 receptor in atopic dermatitis and psoriasis. *BJP*.
 - e) Salaga, M; Polepally, PR; Zielinska, M; Marynowski, M; Fabisiak, A; Murawska, N; Sobczak, K; Sacharczuk, M; Do Rego, JC; Roth, BL. Salvinorin A analogues PR-37 and PR-38 attenuate compound 48/80-induced itch responses in mice. *BJP*
 - f) Flower RJ, *BJP*.
 - g) Spyra, Stefan; Meisner, Anne; Schaefer, Michael; Hill, Kerstin. COX-2-selective inhibitors celecoxib and deracoxib positively modulate TRPV3 channels. *BJP*
- 2) Bissonnette R, Maari C, Forman S, et al. The oral Janus kinase/spleen tyrosine kinase inhibitor ASN002 demonstrates efficacy and improves associated systemic inflammation in patients with moderate-to-severe atopic dermatitis: results from a randomized double-blind placebo-controlled study. *Br J Dermatol* 2019 Mar. doi: 10.1111/bjd.17932. [Epub ahead of print]
- 3) Yosipovitch G, Reaney M, Mastey V, et al. Peak Pruritus Numerical Rating Scale: Psychometric Validation and Responder Definition for Assessing Itch in Moderate-To-Severe Atopic Dermatitis. *Br J Dermatol* 2019. doi: 10.1111/bjd.17744. [Epub ahead of print]
- 4) Silverberg JI, Gelfand JM, Margolis DJ, et al. Symptoms and diagnosis of anxiety and depression in atopic dermatitis in U.S. *Br J Dermatol* 2019. doi: 10.1111/bjd.17683. [Epub ahead of print]
- 5) Hussain AB, Samuel R, Hegade VS, et al. Pruritus Secondary to Primary Biliary Cholangitis: A Review of the Pathophysiology and Management with Phototherapy. *Br J Dermatol* 2019. doi: 10.1111/bjd.17933. [Epub ahead of print]
- 6) de Wijs LEM, Bosma AL, Eler NS, et al. Effectiveness of dupilumab treatment in 95 patients with atopic dermatitis: daily practice data. *Br J Dermatol* 2019. doi: 10.1111/bjd.18179. [Epub ahead of print]
- 7) Cenzer I, Nkansah-Mahaney N, Wehner M, et al. A Multi Year Cross Sectional Study of US National Prescribing Patterns of First Generation Sedating Antihistamines in Older Adults with Skin Disease. *Br J Dermatol* 2019. doi: 10.1111/bjd.18042. [Epub ahead of print]