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 H_4 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.

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