(*e.g.*, degenerative joint disease), throat conditions (*e.g.*, dysphagia or spasmodic dysphonias), tactile sensitivity, electrolyte imbalance and/or vitamin deficiency, respiratory conditions (*e.g.*, asthma), cough, and sarcoidosis. As shown herein, compositions that include activators of ion channels (*e.g.,* TRP or ASIC channels) may be useful to treat the above-mentioned conditions.

SUMMARY OF THE INVENTION

In one aspect, the present disclosure relates to a composition formulated for oral administration, said composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient, wherein said composition is a liquid or solid, and wherein said composition is formulated for delayed release of said ion channel activator. In an embodiment, the present disclosure features a composition formulated for oral administration, said composition comprising an effective amount of an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof). In some embodiments, the composition comprises a plurality of (*e.g.*, two or three) ion channel activators (*e.g.*, TRPV1 channel activators, TRPA1 channel activators, ASIC channel activators, or combinations thereof). In some embodiments, the composition further comprises a pharmaceutically acceptable excipient. In some embodiments, the composition further comprises a plurality of pharmaceutically acceptable excipients.

In some embodiments, the composition is formulated for modified release (*e.g.*, delayed release, extended release, or rapid release) of said ion channel activator (*e.g.*, TRPV1 channel activator, TRPA1 channel activator, ASIC channel activator, or combination thereof). In some embodiments, said pharmaceutically acceptable excipient comprises an agent for modified release (*e.g.*, delayed release, extended release, or rapid release) of an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof), such that, when orally administered to a subject, the ion channel activator (*e.g.*, TRPV1 channel activator, TRPA1 channel activator, ASIC channel activator, or combination thereof) is not substantially released in the stomach of said subject. In some embodiments, the agent for modified release (*e.g.*, delayed release, extended release, or rapid release) is selected from the group consisting of: hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, carboxymethyl cellulose, and mixtures thereof.

In some embodiments, said pharmaceutically acceptable excipient comprises a coating. In some embodiments, said coating is selected from the group consisting of: enteric coatings, sugar coatings, and polymeric coatings. In some embodiments, said ion channel activator (*e.g.*, TRPV1

channel activator, TRPA1 channel activator, ASIC channel activator, or combination thereof) is embedded in biodegradable microparticles or nanoparticles for sustained release.

In some embodiments, the composition further comprises a formulation base. In some embodiments, the formulation base comprises an oil and a lipophilic additive. In some embodiments, said oil is selected from the group consisting of: vegetable oil, mineral oil, soya oil, sunflower oil, corn oil, olive oil, nut oil, and liquid paraffin. In some embodiments, said lipophilic additive is selected from the group consisting of: polyethylene glycol, fatty acid mono-, di-, or triglycerides, palmitic acid, stearic acid, behenic acid, polyethylene glycol fatty acid esters, candelilla wax, carnauba wax, polyethylene oxide wax, and petroleum wax. In some embodiments, the composition further comprises a coloring agent, a dissolving agent, a flavoring agent, a sweetener, a viscosity modifier, an electrolyte, a vitamin, a mineral, an antioxidant, or a preservative.

In any embodiment of the disclosure, the TRPV1 channel activator is a capsaicinoid, a capsinoid, oleoylethanolamide, N-oleoyldopamine, 3-methyl-N-oleoyldopamine, oleamide, capsiate, a 1-monoacylglycerol having C18 and C20 unsaturated and C8-C12 saturated fatty acids, a 2- monoacylglycerol having C18 and C20 unsaturated fatty acids, miogadial, miogatrial, polygodial, a terpenoid with an alpha,beta-unsaturated 1,4-dialdehyde moiety, sanshool, evodiamine, acesulfame-K, cyclamate, $CuSO_4$, $ZnSO_4$, $FeSO_4$, arvanil, anandamide, N-arachidonoyl-dopamine, flufenamic acid dopamide, a dopamine amide of fenamic acid, 4-hydroxynonenal, 1-[2-(1-adamantyl)ethyl]-1-pentyl-3-[3-(4-pyridyl)propyl]urea, or gingerol.

In particular embodiments, the capsaicinoid is capsaicin. In some embodiments, the TRPV1 channel activator is present from about 0.001% to about 10% (w/w) or from about 0.001% to about 10% (v/v).

In some embodiments, the TRPV1 channel activator is naturally occurring or non-naturally occurring. In some embodiments, said naturally occurring TRPV1 channel activator is selected from the group consisting of: capsaicin, dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin, homocapsaicin, nonivamide, pseudocapsaicin, resiniferatoxin, tinyatoxin, capsiate, dihydrocapsiate, nordihydrocapsiate, norcapsaicin, capsiconiate, dihydrocapsiconiate and other coniferyl esters, capsiconinoid, and 3-hydroxyacetanilide.

In some embodiments, the non-naturally occurring TRPV1 channel activator is selected from the group consisting of: 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl

formate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl acetate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl propanoate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl butanoate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methoxyphenyl 2,2-dimethylpropanoate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl octadecanoate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl{4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methoxyphenoxy}formate, homovanillyl 8-methylnonanoate, 3-(3-methoxy-4-hydroxyphenyl)propyl 8-methylnonanoate, 8-methylnonyl homovanillate, 8-methylnonanoic acid-substituted benzyl ester derivative, heptanoyl isobutylamide, heptanoyl guaiacylamide, 7-phenylhept-6-yne-acid-4-hydroxy-3-methoxybenzylamide, dohevanil, denatonium capsaicinate, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(4-chlorophenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(4-fluorophenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(2,4-dichlorophenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(4-benzyloxyphenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(4-(N-octyloxy)phenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[4-N-octyloxybenzyl]thiourea, N-phenylmethylalkynamide capsaicin derivatives, N-(4-O-glycerol-3-methoxybenzyl)nonamide, N-nonanoyl vanillylamide-4-glyceryl ether, N-(4-O-acetic acid sodium)-3-methoxybenzyl-nonamide (sodium N-nonanoyl vanillylamide-4-O-acetate), N-(4-O-glycol-3-methoxybenzyl)-nonamide (N-nonanoyl vanillylamide-4-glycol ether), 20-homovanillyl-mezerein, 20-homovanillyl-12-deoxyphorbol-13-phenylacetate), civamide (N-[(4-hydroxy-3-methoxyphenyl)-methyl]-8-methyl-(Z)-6-nonemamide), nuvanil, capsavanil, olvanil, arvanil, and palvanil (N-palmitoyl-vanillamide).

In some embodiments of the disclosure, the TRPA1 channel activator is allyl isothiocyanate, gingerol, cinnamaldehyde, acrolein, farnesyl thiosalicylic acid, Δ_9-tetrahydrocannabinol, eugenol, a shogaol, a sanshool, allicin, diallyl sulfide, diallyl disulfide, diallyl trisulfide, or farnesyl thioacetic acid. In some embodiments, the TRPA1 channel activator is present from about 0.001% to about 10% (w/w) or from about 0.001% to about 10% (v/v).

In some embodiments, the ASIC channel activator comprises acetic acid, phosphoric acid, citric acid, malic acid, succinic acid, lactic acid, tartaric acid, fumaric acid, or ascorbic acid.

mg, about 500 mg, about 750 mg, about 1 g, about 2 g, about 5 g, about 10 g, or more. In some embodiments, an effective amount of the solid formulation is between about 0.5 mg and about 100 mg. In some embodiments, an effective amount of the solid formulation is between about 100 mg and about 500 mg. In some embodiments, an effective amount of the solid formulation is between about 500 mg and about 1000 mg.

In some embodiments, the composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) is formulated for use once a day. In some embodiments, the composition is formulated for use at least about 1 time per day, about 2 times per day, about 3 times per day, about 4 times per day, about 5 times per day, or more. In some embodiments, the composition is formulated for use about 1-3 times per day. In some embodiments, the composition is formulated for use for a period of about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, or more.

In another aspect, the present disclosure relates to a composition formulated for oral administration to a subject, said composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient, wherein upon administration, the ion channel activator has a residence time of greater than about 5 seconds in the mouth of the subject. In an embodiment, the disclosure features a composition formulated for oral administration, said composition comprising an effective amount of an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof), and a pharmaceutically acceptable excipient, wherein said composition is a liquid or solid, and wherein said composition is formulated for delayed release of said ion channel activator (*e.g.*, TRPV1 channel activator, TRPA1 channel activator, ASIC channel activator, or combination thereof). In some embodiments, said composition comprises a plurality of (*e.g.*, two or three) ion channel activators (*e.g.*, TRPV1 channel activators, TRPA1 channel activators, ASIC channel activators, or combinations thereof), and a pharmaceutically acceptable excipient. In some embodiments, said composition comprises an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof), and a plurality of pharmaceutically acceptable excipients.

In some embodiments, said pharmaceutically acceptable excipient comprises an agent for delayed release of an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof), such that, when orally

formulated for use at least about 1 time per day, about 2 times per day, about 3 times per day, about 4 times per day, about 5 times per day, or more. In some embodiments, the composition is formulated for use about 1-3 times per day. In some embodiments, the composition is formulated for use for a period of about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, or more.

In any embodiment of the disclosure, the TRPV1 channel activator is a capsaicinoid, a capsinoid, oleoylethanolamide, N-oleoyldopamine, 3-methyl-N-oleoyldopamine, oleamide, capsiate, a 1-monoacylglycerol having C18 and C20 unsaturated and C8-C12 saturated fatty acid, a 2- monoacylglycerol having C18 and C20 unsaturated fatty acids, miogadial, miogatrial, polygodial, a terpenoid with an alpha,beta-unsaturated 1,4-dialdehyde moiety, sanshool, evodiamine, acesulfame-K, cyclamate, $CuSO_4$, $ZnSO_4$, $FeSO_4$, arvanil, anandamide, N-arachidonoyl-dopamine, flufenamic acid dopamide, a dopamine amide of fenamic acid, 4-hydroxynonenal, 1-[2-(1-adamantyl)ethyl]-1-pentyl-3-[3-(4-pyridyl)propyl]urea, or gingerol.

In particular embodiments, the capsaicinoid is capsaicin. In some embodiments, the TRPV1 channel activator is present from about 0.001% to about 10% (w/w) or from about 0.001% to about 10% (v/v).

In some embodiments, the TRPV1 channel activator is naturally occurring or non-naturally occurring. In some embodiments, said naturally occurring TRPV1 channel activator is selected from the group consisting of: capsaicin, dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin, homocapsaicin, nonivamide, pseudocapsaicin, resiniferatoxin, tinyatoxin, capsiate, dihydrocapsiate, nordihydrocapsiate, norcapsaicin, capsiconiate, dihydrocapsiconiate and other coniferyl esters, capsiconinoid, and 3-hydroxyacetanilide.

In some embodiments, the non-naturally occurring TRPV1 channel activator is selected from the group consisting of: 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl formate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl acetate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl propanoate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl butanoate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methoxyphenyl 2,2-dimethylpropanoate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl octadecanoate, 4-[((6E)-8-methylnon-6-

enoylamino)methyl]-2-methyoxyphenyl{4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methoxyphenoxy}formate, homovanillyl 8-methylnonanoate, 3-(3-methoxy-4-hydroxyphenyl)propyl 8-methylnonanoate, 8-methylnonyl homovanillate, 8-methylnonanoic acid-substituted benzyl ester derivative, heptanoyl isobutylamide, heptanoyl guaiacylamide, 7-phenylhept-6-yne-acid-4-hydroxy-3-methoxybenzylamide, dohevanil, denatonium capsaicinate, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(4-chlorophenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(4-fluorophenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(2,4-dichlorophenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(4-benzyloxyphenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(4-(N-octyloxy)phenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[4-N-octyloxybenzyl]thiourea, N-phenylmethylalkynamide capsaicin derivatives, N-(4-O-glycerol-3-methoxybenzyl)-nonamide, N-nonanoyl vanillylamide-4-glyceryl ether, N-(4-O-acetic acid sodium)-3-methoxybenzyl-nonamide (sodium N-nonanoyl vanillylamide-4-O-acetate), N-(4-O-glycol-3-methoxybenzyl)-nonamide (N-nonanoyl vanillylamide-4-glycol ether), 20-homovanillyl-mezerein, 20-homovanillyl-12-deoxyphorbol-13-phenylacetate), civamide (N-[(4-hydroxy-3-methoxyphenyl)-methyl]-8-methyl-(Z)-6-nonemamide), nuvanil, capsavanil, olvanil, arvanil, and palvanil (N-palmitoyl-vanillamide).

In further embodiments of the disclosure, the TRPA1 channel activator is allyl isothiocyanate, gingerol, cinnamaldehyde, acrolein, farnesyl thiosalicylic acid, Δ_9-tetrahydrocannabinol, eugenol, a shogaol, a sanshool, allicin, diallyl sulfide, diallyl disulfide, diallyl trisulfide, or farnesyl thioacetic acid. In some embodiments, the TRPA1 channel activator is present from about 0.001% to about 10% (w/w) or from about 0.001% to about 10% (v/v).

In some embodiments, the ASIC channel activator comprises acetic acid, phosphoric acid, citric acid, malic acid, succinic acid, lactic acid, tartaric acid, fumaric acid, or ascorbic acid. In some embodiments, the ASIC channel activator is present from about 0.001% to about 10% (w/w) or from about 0.001% to about 10% (v/v).

In some embodiments, the composition is capable of reducing gastrointestinal side effects.

In another embodiment, the disclosure features a composition comprising an effective amount of an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof), a formulation base, and a pharmaceutically acceptable excipient. In some embodiments, said composition comprises a plurality of (*e.g.*, two or three) ion channel activators (*e.g.*, TRPV1 channel activators, TRPA1 channel activators, ASIC channel activators, or combinations thereof), a formulation base, and a pharmaceutically acceptable excipient. In some embodiments, said composition comprises an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof), a formulation base, and a plurality of pharmaceutically acceptable excipients.

In some embodiments, the formulation base comprises an oil and a lipophilic additive. In some embodiments, said oil is selected from the group consisting of: vegetable oil, mineral oil, soya oil, sunflower oil, corn oil, olive oil, nut oil, and liquid paraffin. In some embodiments, said lipophilic additive is selected from the group consisting of: polyethylene glycol, fatty acid mono-, di-, or triglycerides, palmitic acid, stearic acid, behenic acid, polyethylene glycol fatty acid esters, candelilla wax, carnauba wax, polyethylene oxide wax, and petroleum wax. In some embodiments, the composition further comprises a coloring agent, a dissolving agent, a flavoring agent, a sweetener, a viscosity modifier, an electrolyte, a vitamin, a mineral, an antioxidant, or a preservative.

In some embodiments, the composition is formulated as a liquid or a solid. In some embodiments, the composition is formulated as a liquid. In some embodiments, the liquid is selected from the group consisting of emulsions, microemulsions, solutions, suspensions, syrups (*e.g.*, syrup concentrates), linctuses, drops, sprays, and elixirs. In some embodiments, the composition is formulated as a solid. In some embodiments, the solid is selected from the group consisting of tablets, capsules, powders, crystals, pastes, gels, lozenges (*e.g.*, liquid filled lozenges), gums, candies, chews, foodstuffs, dissolving strips, films, and semi-solid formulations. In some embodiments, said solid is a tablet or capsule. In some embodiments, said capsule is a hard or soft capsule.

In some embodiments, the composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) is formulated for use once a day. In some embodiments, the composition is

formulated for use at least about 1 time per day, about 2 times per day, about 3 times per day, about 4 times per day, about 5 times per day, or more. In some embodiments, the composition is formulated for use about 1-3 times per day. In some embodiments, the composition is formulated for use for a period of about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, or more.

In any embodiment of the disclosure, the TRPV1 channel activator is a capsaicinoid, a capsinoid, oleoylethanolamide, N-oleoyldopamine, 3-methyl-N-oleoyldopamine, oleamide, capsiate, a 1-monoacylglycerol having C18 and C20 unsaturated and C8-C12 saturated fatty acid, a 2- monoacylglycerol having C18 and C20 unsaturated fatty acids, miogadial, miogatrial, polygodial, a terpenoid with an alpha,beta-unsaturated 1,4-dialdehyde moiety, sanshool, evodiamine, acesulfame-K, cyclamate, $CuSO_4$, $ZnSO_4$, $FeSO_4$, arvanil, anandamide, N-arachidonoyl-dopamine, flufenamic acid dopamide, a dopamine amide of fenamic acid, 4-hydroxynonenal, 1-[2-(1-adamantyl)ethyl]-1-pentyl-3-[3-(4-pyridyl)propyl]urea, or gingerol.

In particular embodiments, the capsaicinoid is capsaicin. In some embodiments, the TRPV1 channel activator is present from about 0.001% to about 10% (w/w) or from about 0.001% to about 10% (v/v).

In some embodiments, the TRPV1 channel activator is naturally occurring or non-naturally occurring. In some embodiments, said naturally occurring TRPV1 channel activator is selected from the group consisting of: capsaicin, dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin, homocapsaicin, nonivamide, pseudocapsaicin, resiniferatoxin, tinyatoxin, capsiate, dihydrocapsiate, nordihydrocapsiate, norcapsaicin, capsiconiate, dihydrocapsiconiate and other coniferyl esters, capsiconinoid, and 3-hydroxyacetanilide.

In some embodiments, the non-naturally occurring TRPV1 channel activator is selected from the group consisting of: 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl formate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl acetate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl propanoate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl butanoate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methoxyphenyl 2,2-dimethylpropanoate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl octadecanoate, 4-[((6E)-8-methylnon-6-

enoylamino)methyl]-2-methyoxyphenyl{4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methoxyphenoxy}formate, homovanillyl 8-methylnonanoate, 3-(3-methoxy-4-hydroxyphenyl)propyl 8-methylnonanoate, 8-methylnonyl homovanillate, 8-methylnonanoic acid-substituted benzyl ester derivative, heptanoyl isobutylamide, heptanoyl guaiacylamide, 7-phenylhept-6-yne-acid-4-hydroxy-3-methoxybenzylamide, dohevanil, denatonium capsaicinate, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(4-chlorophenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(4-fluorophenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(2,4-dichlorophenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(4-benzyloxyphenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(4-(n-octyloxy)phenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[4-N-octyloxybenzyl]thiourea, N-phenylmethylalkynamide capsaicin derivatives, N-(4-O-glycerol-3-methoxybenzyl)-nonamide, N-nonanoyl vanillylamide-4-glyceryl ether, N-(4-O-acetic acid sodium)-3-methoxybenzyl-nonamide (sodium N-nonanoyl vanillylamide-4-O-acetate), N-(4-O-glycol-3-methoxybenzyl)-nonamide (N-nonanoyl vanillylamide-4-glycol ether), 20-homovanillyl-mezerein, 20-homovanillyl-12-deoxyphorbol-13-phenylacetate), civamide (N-[(4-hydroxy-3-methoxyphenyl)-methyl]-8-methyl-(Z)-6-nonemamide), nuvanil, capsavanil, olvanil, arvanil, and palvanil (N-palmitoyl-vanillamide).

In further embodiments of the disclosure, the TRPA1 channel activator is allyl isothiocyanate, gingerol, cinnamaldehyde, acrolein, farnesyl thiosalicylic acid, Δ_9-tetrahydrocannabinol, eugenol, a shogaol, a sanshool, allicin, diallyl sulfide, diallyl disulfide, diallyl trisulfide, or farnesyl thioacetic acid. In some embodiments, the TRPA1 channel activator is present from about 0.001% to about 10% (w/w) or from about 0.001% to about 10% (v/v).

In some embodiments, the ASIC channel activator comprises acetic acid, phosphoric acid, citric acid, malic acid, succinic acid, lactic acid, tartaric acid, fumaric acid, or ascorbic acid. In some embodiments, the ASIC channel activator is present from about 0.001% to about 10% (w/w) or from about 0.001% to about 10% (v/v).

In some embodiments, the composition is capable of reducing gastrointestinal side effects.

In another embodiment, the disclosure features a composition formulated for oral administration to a subject, said composition comprising an effective amount of an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) and a pharmaceutically acceptable excipient, wherein upon administration, the ion channel activator has a residence time of greater than about 5 seconds in the mouth of the subject. In some embodiments, said composition comprises a plurality of (*e.g.*, two or three) ion channel activators (*e.g.*, TRPV1 channel activators, TRPA1 channel activators, ASIC channel activators, or combinations thereof) and a pharmaceutically acceptable excipient. In some embodiments, said composition comprises an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) and a plurality of pharmaceutically acceptable excipients.

In some embodiments, the ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) has a residence time of greater than about 5 seconds in the mouth of a subject, *e.g.*, greater than about 6 seconds, about 7 seconds, about 8 seconds, about 9 seconds, about 10 seconds, about 11 seconds, about 12 seconds, about 13 seconds, about 14 seconds, about 15 seconds, about 20 seconds, about 25 seconds, about 30 seconds, about 45 seconds, about 60 seconds, about 90 seconds, about 2 minutes, about 3 minutes, about 4 minutes, about 5 minutes, or more. In some embodiments, the ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) has a residence time in the mouth of a subject between about 5 seconds and about 2 minutes. In some embodiments, the ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) has a residence time in the mouth of a subject between about 5 seconds and about 60 seconds. In some embodiments, the ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) has a residence time in the mouth of a subject between about 5 seconds and about 30 seconds.

In some embodiments, the ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) has a residence time of greater than about 60 seconds in the mouth of a subject, *e.g.*, greater than about 90 seconds, about 2 minutes, about 3 minutes, about 4 minutes, about 5 minutes, about 6 minutes, about 7 minutes, about 8 minutes, about 9 minutes, about 10 minutes, or more. In some

embodiments, the ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) has a residence time in the mouth of a subject between about 60 seconds and about 5 minutes. In some embodiments, the ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) has a residence time in the mouth of a subject between about 60 seconds and about 3 minutes. In some embodiments, the ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) has a residence time in the mouth of a subject between about 60 seconds and about 2 minutes.

In some embodiments, the composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) is formulated for use once a day. In some embodiments, the composition is formulated for use at least about 1 time per day, about 2 times per day, about 3 times per day, about 4 times per day, about 5 times per day, or more. In some embodiments, the composition is formulated for use about 1-3 times per day. In some embodiments, the composition is formulated for use for a period of about 1 day, about 2 days, about 3 days, about 4 days, about 5 days, about 6 days, about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, or more.

In some embodiments, the composition further comprises a formulation base. In some embodiments, the formulation base comprises an oil and a lipophilic additive. In some embodiments, said oil is selected from the group consisting of: vegetable oil, mineral oil, soya oil, sunflower oil, corn oil, olive oil, nut oil, and liquid paraffin. In some embodiments, said lipophilic additive is selected from the group consisting of: polyethylene glycol, fatty acid mono-, di-, or triglycerides, palmitic acid, stearic acid, behenic acid, polyethylene glycol fatty acid esters, candelilla wax, carnauba wax, polyethylene oxide wax, and petroleum wax. In some embodiments, the composition further comprises a coloring agent, a dissolving agent, a flavoring agent, a sweetener, a viscosity modifier, an electrolyte, a vitamin, a mineral, an antioxidant, or a preservative.

In any embodiment of the disclosure, the TRPV1 channel activator is a capsaicinoid, a capsinoid, oleoylethanolamide, N-oleoyldopamine, 3-methyl-N-oleoyldopamine, oleamide,

capsiate, a 1-monoacylglycerol having C18 and C20 unsaturated and C8-C12 saturated fatty acid, a 2- monoacylglycerol having C18 and C20 unsaturated fatty acids, miogadial, miogatrial, polygodial, a terpenoid with an alpha,beta-unsaturated 1,4-dialdehyde moiety, sanshool, evodiamine, acesulfame-K, cyclamate, $CuSO_4$, $ZnSO_4$, $FeSO_4$, arvanil, anandamide, N-arachidonoyl-dopamine, flufenamic acid dopamide, a dopamine amide of fenamic acid, 4-hydroxynonenal, 1-[2-(1-adamantyl)ethyl]-1-pentyl-3-[3-(4-pyridyl)propyl]urea, or gingerol.

In particular embodiments, the capsaicinoid is capsaicin. In some embodiments, the TRPV1 channel activator is present from about 0.001% to about 10% (w/w) or from about 0.001% to about 10% (v/v).

In some embodiments, the TRPV1 channel activator is naturally occurring or non-naturally occurring. In some embodiments, said naturally occurring TRPV1 channel activator is selected from the group consisting of: capsaicin, dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin, homocapsaicin, nonivamide, pseudocapsaicin, resiniferatoxin, tinyatoxin, capsiate, dihydrocapsiate, nordihydrocapsiate, norcapsaicin, capsiconiate, dihydrocapsiconiate and other coniferyl esters, capsiconinoid, and 3-hydroxyacetanilide.

In some embodiments, the non-naturally occurring TRPV1 channel is selected from the group consisting of: 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl formate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl acetate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl propanoate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl butanoate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methoxyphenyl 2,2-dimethylpropanoate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl octadecanoate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl{4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methoxyphenoxy}formate, homovanillyl 8-methylnonanoate, 3-(3-methoxy-4-hydroxyphenyl)propyl 8-methylnonanoate, 8-methylnonyl homovanillate, 8-methylnonanoic acid-substituted benzyl ester derivative, heptanoyl isobutylamide, heptanoyl guaiacylamide, 7-phenylhept-6-yne-acid-4-hydroxy-3-methoxybenzylamide, dohevanil, denatonium capsaicinate, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(4-chlorophenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(4-fluorophenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(2,4-dichlorophenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(4-benzyloxyphenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-

methoxybenzyl]-N'-[2-(4-(N-octyloxy)phenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[4-N-octyloxybenzyl]thiourea, N-phenylmethylalkynamide capsaicin derivatives, N-(4-O-glycerol-3-methoxybenzyl)nonamide, N-nonanoyl vanillylamide-4-glyceryl ether, N-(4-O-acetic acid sodium)-3-methoxybenzyl-nonamide, sodium N-nonanoyl vanillylamide-4-O-acetate), N-(4-O-glycol-3-methoxybenzyl)-nonamide, N-nonanoyl vanillylamide-4-glycol ether), 20-homovanillyl-mezerein, 20-homovanillyl-12-deoxyphorbol-13-phenylacetate), civamide (N-[(4-hydroxy-3-methoxyphenyl)-methyl]-8-methyl-(Z)-6-nonemamide), nuvanil, capsavanil, olvanil, arvanil, and palvanil (N-palmitoyl-vanillamide).

In some embodiments of the disclosure, the TRPA1 channel activator is allyl isothiocyanate, a gingerol, cinnamaldehyde, acrolein, farnesyl thiosalicylic acid, Δ_9-tetrahydrocannabinol, eugenol, a shogaol, a sanshool, allicin, diallyl sulfide, diallyl disulfide, diallyl trisulfide, or farnesyl thioacetic acid. In some embodiments, the TRPA1 channel activator is present from about 0.001% to about 10% (w/w) or from about 0.001% to about 10% (v/v).

In some embodiments, the ASIC channel activator comprises acetic acid, phosphoric acid, citric acid, malic acid, succinic acid, lactic acid, tartaric acid, fumaric acid, or ascorbic acid. In some embodiments, the ASIC channel activator is present from about 0.001% to about 10% (w/w) or from about 0.001% to about 1% (v/v).

In some embodiments, the composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) comprises a liquid or solid formulation. In some embodiments, the liquid formulation is selected from the group consisting of emulsions, microemulsions, solutions, suspensions, syrups (*e.g.*, syrup concentrates), linctuses, drops, sprays, and elixirs. In some embodiments, the solid formulation is selected from the group consisting of tablets, capsules, powders, crystals, pastes, gels, lozenges (*e.g.*, liquid filled lozenges), gums, candies, chews, foodstuffs, dissolving strips, films, and semi-solid formulations. In some embodiments, said solid formulation is a tablet or capsule. In some embodiments, said capsule is a hard or soft capsule.

In some embodiments, the ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) comprises about 0.01% or more of a liquid formulation, *e.g.*, about 0.02%, about 0.03%, about 0.04%, about

In another aspect, the present disclosure relates to the use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient in the manufacture of a medicament, for treating a painful muscle contraction in a subject in need thereof. In an embodiment, the disclosure features a method of treating a painful muscle contraction in a subject in need thereof, said method comprising orally administering to said subject a composition comprising an effective amount of an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) and a pharmaceutically acceptable excipient. In some embodiments, said method comprises orally administering to a subject a composition comprising a plurality of (*e.g.*, two or three) ion channel activators (*e.g.*, TRPV1 channel activators, TRPA1 channel activators, ASIC channel activators, or combinations thereof) and a pharmaceutically acceptable excipient. In some embodiments, said method comprises orally administering to a subject a composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) and a plurality of pharmaceutically acceptable excipients. In some embodiments, said painful muscle contraction is a muscle contraction of the head or neck. In some embodiments, said painful muscle contraction is associated with tension headache, cluster headache, or migraine headache.

In another aspect, the present disclosure relates to the use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient in the manufacture of a medicament, for treating tactile sensitivity in a subject in need thereof. In an embodiment, the disclosure features a method of treating tactile sensitivity in a subject in need thereof, said method comprising orally administering to said subject a composition comprising an effective amount of an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) and a pharmaceutically acceptable excipient. In some embodiments, said method comprises orally administering to a subject a composition comprising a plurality of (*e.g.*, two or three) ion channel activators (*e.g.*, TRPV1 channel activators, TRPA1 channel activators, ASIC channel activators, or combinations thereof) and a pharmaceutically acceptable excipient. In some embodiments, said method comprises orally administering to a subject a composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) and a plurality of pharmaceutically acceptable excipients. In some embodiments, said tactile sensitivity is associated with autism, dyspraxia, neuralgia, anxiety disorders, venomous bites, or venomous stings. In some embodiments, said anxiety disorder is selected from the group consisting of panic disorder, obsessive-compulsive disorder

(OCD), post-traumatic stress disorder (PTSD), social anxiety disorder, phobia, and generalized anxiety disorder (GAD).

In another aspect, the present disclosure relates to the use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient in the manufacture of a medicament, for treating a dystonia in a subject in need thereof. In an embodiment, the disclosure features a method of treating a dystonia in a subject in need thereof, said method comprising orally administering to said subject a composition comprising an effective amount of an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) and a pharmaceutically acceptable excipient. In some embodiments, said method comprises orally administering to a subject a composition comprising a plurality of (*e.g.*, two or three) ion channel activators (*e.g.*, TRPV1 channel activators, TRPA1 channel activators, ASIC channel activator, or combinations thereof) and a pharmaceutically acceptable excipient. In some embodiments, said method comprises orally administering to a subject a composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) and a plurality of pharmaceutically acceptable excipients. In some embodiments, said dystonia is selected from the group consisting of: focal dystonia, blepharospasm, cervical dystonia, cranial dystonia, laryngeal dystonia, back spasms, hand dystonia, or leg cramps due to spinal stenosis.

In another aspect, the present disclosure relates to the use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient in the manufacture of a medicament, for treating a peripheral nervous system (PNS) condition in a subject in need thereof. In an embodiment, the disclosure features a method of treating a peripheral nervous system (PNS) condition in a subject in need thereof, said method comprising orally administering to said subject a composition comprising an effective amount of an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) and a pharmaceutically acceptable excipient to said subject. In some embodiments, said method comprises orally administering to a subject a composition comprising a plurality of (*e.g.*, two or three) ion channel activators (*e.g.*, TRPV1 channel activators, TRPA1 channel activators, ASIC channel activators, or combinations thereof) and a pharmaceutically acceptable excipient. In some embodiments, said method comprises orally administering to a subject a composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) and a plurality of pharmaceutically acceptable excipients. In some embodiments, said PNS condition is selected from the group

consisting of: cramp fasciculation syndrome, Isaacs' Syndrome or neuromyotonia (NMT), peripheral neuropathy, carpal tunnel syndrome, and Epstein-Barr virus (EBV) infection.

In another aspect, the present disclosure relates to the use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient in the manufacture of a medicament, for treating a throat condition in a subject in need thereof. In an embodiment, the disclosure features a method of treating a throat condition in a subject in need thereof, said method comprising orally administering to said subject a composition comprising an effective amount of an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) and a pharmaceutically acceptable excipient. In some embodiments, said method comprises orally administering to a subject a composition comprising a plurality of (*e.g.*, two or three) ion channel activators (*e.g.*, TRPV1 channel activators, TRPA1 channel activators, ASIC channel activators, or combinations thereof) and a pharmaceutically acceptable excipient. In some embodiments, said method comprises orally administering to a subject a composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) and a plurality of pharmaceutically acceptable excipients. In some embodiments, said throat condition is associated with chemical injury, cancer, surgical injury, or pathogen infection. In some embodiments, said throat condition is selected from the group consisting of: acid reflux, laryngospasm, dysphagia, and spasmodic dysphonias.

In another aspect, the present disclosure relates to the use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient in the manufacture of a medicament, for treating a condition associated with an electrolyte imbalance or vitamin deficiency in a subject in need thereof. In an embodiment, the disclosure features a method of treating a condition associated with an electrolyte imbalance or vitamin deficiency in a subject in need thereof, said method comprising orally administering to said subject a composition comprising an effective amount of an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) and a pharmaceutically acceptable excipient. In some embodiments, said method comprises orally administering to a subject a composition comprising a plurality of (*e.g.*, two or three) ion channel activators (*e.g.*, TRPV1 channel activators, TRPA1 channel activators, ASIC channel activators, or combinations thereof) and a pharmaceutically acceptable excipient. In some embodiments, said method comprises orally administering to a subject a composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) and a plurality of pharmaceutically acceptable excipients. In some embodiments, said condition is selected from the group consisting of: hyponatremia, kidney disease, rickets, calcium, magnesium deficiency,

thiamine deficiency, hypoparathyroidism, medullary cystic disease, and adrenocortical carcinoma.

In another aspect, the present disclosure relates to the use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient in the manufacture of a medicament, for treating a central nervous system (CNS) condition in a subject in need thereof. In an embodiment, the disclosure features a method of treating a central nervous system (CNS) condition in a subject in need thereof, said method comprising orally administering to said subject a composition comprising an effective amount of an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) and a pharmaceutically acceptable excipient. In some embodiments, said method comprises orally administering to a subject a composition comprising a plurality of (*e.g.*, two or three) ion channel activators (*e.g.*, TRPV1 channel activators, TRPA1 channel activators, ASIC channel activators, or combination thereof) and a pharmaceutically acceptable excipient. In some embodiments, said method comprises orally administering to a subject a composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) and a plurality of pharmaceutically acceptable excipients. In some embodiments, said CNS condition is associated with a tumor. In some embodiments, said CNS condition is selected from the group consisting of: multiple sclerosis, amyotrophic lateral sclerosis, cerebral palsy, stroke, motor neuron disease, spinal injury, and stenosis.

In another aspect, the present disclosure relates to the use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient in the manufacture of a medicament, for treating a muscle condition or disorder in a subject in need thereof. In an embodiment, the disclosure features a method of treating a muscle condition or disorder in a subject in need thereof, said method comprising orally administering to said subject a composition comprising an effective amount of an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) and a pharmaceutically acceptable excipient. In some embodiments, said method comprises orally administering to a subject a composition comprising a plurality of (*e.g.*, two or three) ion channel activators (*e.g.*, TRPV1 channel activators, TRPA1 channel activators, ASIC channel activators, or combinations thereof) and a pharmaceutically acceptable excipient. In some embodiments, said method comprises orally administering to a subject a composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) and a plurality of pharmaceutically acceptable excipients. In some embodiments, said muscle condition is associated with muscle

pain, muscle spasms, muscle cramps, fasciculations, or any combination thereof. In some embodiments, the muscle condition or disorder is a neuromuscular disorder (*e.g.*, multiple sclerosis, spinal cord spasticity, spinal muscle atrophy, myasthenia gravis, spinal cord injury, traumatic brain injury, cerebral palsy, hereditary spastic paraplegia, motor neuron disease (*e.g.*, amyotrophic lateral sclerosis, primary lateral sclerosis, progressive muscular atrophy, progressive bulbar palsy, pseudobulbar palsy, spinal muscular atrophy, progressive spinobulbar muscular atrophy (*e.g.*, Kennedy's disease), or post-polio syndrome), neuralgia, fibromyalgia, Machado-Joseph disease, cramp fasciculation syndrome, carpal tunnel syndrome, acrodynia, neurofibromatosis, neuromyotonias (*e.g.*, focal neuromyotonia, Isaacs' syndrome), peripheral neuropathy, piriformis syndrome, plexopathy (*e.g.*, Brachial plexopathy or Lumbosacral plexobathy), radiculopathy (*e.g.*, lower lumbar radiculopathy), and encephalitis).

In some embodiments, said muscle condition is muscle pain, muscle spasms, muscle cramps, spasticity, or fasciculations associated with motor neuron disease (*e.g.*, amyotrophic lateral sclerosis, primary lateral sclerosis, progressive muscular atrophy, progressive bulbar palsy, pseudobulbar palsy, spinal muscular atrophy, progressive spinobulbar muscular atrophy (*e.g.*, Kennedy's disease), or post-polio syndrome).

In some embodiments, said muscle condition is associated with treatment of said subject with dialysis, diuretics, β-blockers, statins, fibrates, β2-agonists, ACE inhibitors, ARBs, anti-psychotic medications, or any combination thereof. In some embodiments, said muscle condition is associated with treatment of said subject with statins and fibrates. In some embodiments, said muscle condition occurs in one or more skeletal muscles. In some embodiments, said muscle condition is refractory to an approved treatment. In some embodiments, said approved treatment is botox, cyclopenzaprine, orphenadrine, baclofen, or any combination thereof. In some embodiments, said muscle condition is fibromyalgia. In some embodiments, said muscle condition involves muscle claudication pain. In some embodiments, said muscle claudication pain is associated with inactivity, restriction, economy class syndrome, paralysis, peripheral artery disease, or immobilization.

In another aspect, the present disclosure relates to the use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient in the manufacture of a medicament, for treating a respiratory condition in a subject in need thereof. In an embodiment, the disclosure features a method of treating a respiratory condition in a subject in need thereof, said method comprising orally administering to said subject a composition comprising an effective amount of an ion channel activator (*e.g.*, a TRPV1 channel

activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) and a pharmaceutically acceptable excipient. In some embodiments, said method comprises orally administering to a subject a composition comprising a plurality of (*e.g.*, two or three) ion channel activators (*e.g.*, TRPV1 channel activators, TRPA1 channel activators, ASIC channel activators, or combination thereof) and a pharmaceutically acceptable excipient. In some embodiments, said method comprises orally administering to a subject a composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) and a plurality of pharmaceutically acceptable excipients. In some embodiments, said respiratory condition comprises asthma, chronic obstructive pulmonary disease, bronchitis, emphysema, pneumonia, cystic fibrosis, influenza, or a cold.

In another aspect, the present disclosure relates to the use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient in the manufacture of a medicament, for treating cough in a subject in need thereof. In an embodiment, the disclosure features a method of treating a cough in a subject in need thereof, said method comprising orally administering to said subject a composition comprising an effective amount of an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof), and a pharmaceutically acceptable excipient. In some embodiments, said method comprises orally administering to a subject a composition comprising a plurality of (*e.g.*, two or three) ion channel activators (*e.g.*, TRPV1 channel activators, TRPA1 channel activators, ASIC channel activators, or combination thereof), and a pharmaceutically acceptable excipient. In some embodiments, said method comprises orally administering to a subject a composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof), and a plurality of pharmaceutically acceptable excipients. In some embodiments, said cough is associated with a respiratory condition (*e.g.*, asthma, chronic obstructive pulmonary disease, bronchitis, emphysema, pneumonia, cystic fibrosis, influenza, or a cold), exposure to an allergen, or inflammation.

In another aspect, the present disclosure relates to the use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient in the manufacture of a medicament, for treating sarcoidosis in a subject in need thereof. In an embodiment, the disclosure features a method of treating sarcoidosis in a subject in need thereof, said method comprising orally administering to said subject a composition comprising an effective amount an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof), and a pharmaceutically acceptable excipient. In some embodiments, said method comprises orally

administering to a subject a composition comprising a plurality of (*e.g.*, two or three) ion channel activators (*e.g.*, TRPV1 channel activators, TRPA1 channel activators, ASIC channel activators, or combinations thereof), and a pharmaceutically acceptable excipient. In some embodiments, said method comprises orally administering to a subject a composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof), and a plurality of pharmaceutically acceptable excipients.

In another aspect, the present disclosure relates to the use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient in the manufacture of a medicament, for treating a connective tissue disease in a subject in need thereof. In an embodiment, the disclosure features a method of treating a connective tissue disease in a subject in need thereof, said method comprising orally administering to said subject a composition comprising an effective amount an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof), and a pharmaceutically acceptable excipient. In some embodiments, said method comprises orally administering to a subject a composition comprising a plurality of (*e.g.*, two or three) ion channel activators (*e.g.*, TRPV1 channel activators, TRPA1 channel activators, ASIC channel activators, or combinations thereof), and a pharmaceutically acceptable excipient. In some embodiments, said method comprises orally administering to a subject a composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof), and a plurality of pharmaceutically acceptable excipients. In some embodiments, said connective tissue disease is selected from the group consisting of Ehlers-Danlos syndrome, epidermolysis bullosa, Marfan syndrome, osteogenesis imperfect, arthritis, scleroderma, Sjögren's syndrome, lupus, vasculitis, mixed connective tissue disease, cellulitis, polymyositis, and dermatomyositis. In some embodiments, said arthritis is rheumatoid arthritis, osteoarthritis, gout, or psioratic arthritis, or wherein said vasculitis is Wegener's granulomatosis or Churg-Strauss Syndrome.

In some embodiments, the method of treatment comprises orally administering to a subject a composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof), wherein said TRPV1 channel activator is capsaicin, a capsaicinoid, or a capsinoid, or is selected from the group consisting of oleoylethanolamide, N-oleoyldopamine, 3-methyl-N-oleoyldopamine, oleamide, capsiate, a 1-monoacylglycerol having C18 and C20

unsaturated and C8-C12 saturated fatty acid, a 2- monoacylglycerol having C18 and C20 unsaturated fatty acids, miogadial, miogatrial, polygodial, a terpenoid with an alpha,beta-unsaturated 1,4-dialdehyde moiety, sanshool, evodiamine, acesulfame-K, cyclamate, $CuSO_4$, $ZnSO_4$, $FeSO_4$, arvanil, anandamide, N-arachidonoyl-dopamine, flufenamic acid dopamide, a dopamine amide of fenamic acid, 4-hydroxynonenal, or 1-[2-(1-adamantyl)ethyl]-1-pentyl-3-[3-(4-pyridyl)propyl]urea, gingerol, and salts of magnesium.

In particular embodiments, the capsaicinoid is capsaicin. In some embodiments, the TRPV1 channel activator is present from about 0.001% to about 10% (w/w) or from about 0.001% to about 10% (v/v).

In some embodiments, the TRPV1 channel activator is naturally occurring or non-naturally occurring. In some embodiments, said naturally occurring TRPV1 channel activator is selected from the group consisting of: capsaicin, dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin, homocapsaicin, nonivamide, pseudocapsaicin, resiniferatoxin, tinyatoxin, capsiate, dihydrocapsiate, nordihydrocapsiate, norcapsaicin, capsiconiate, dihydrocapsiconiate and other coniferyl esters, capsiconinoid, and 3-hydroxyacetanilide.

In some embodiments, the non-naturally occurring TRPV1 channel is selected from the group consisting of: 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl formate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl acetate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl propanoate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl butanoate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methoxyphenyl 2,2-dimethylpropanoate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl octadecanoate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl{4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methoxyphenoxy}formate, homovanillyl 8-methylnonanoate, 3-(3-methoxy-4-hydroxyphenyl)propyl 8-methylnonanoate, 8-methylnonyl homovanillate, 8-methylnonanoic acid-substituted benzyl ester derivative, heptanoyl isobutylamide, heptanoyl guaiacylamide, 7-phenylhept-6-yne-acid-4-hydroxy-3-methoxybenzylamide, dohevanil, denatonium capsaicinate, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(4-chlorophenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(4-fluorophenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(2,4-dichlorophenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(4-benzyloxyphenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-

methoxybenzyl]-N'-[2-(4-(N-octyloxy)phenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[4-N-octyloxybenzyl]thiourea, N-phenylmethylalkynamide capsaicin derivatives, N-(4-O-glycerol-3-methoxybenzyl)nonamide, N-nonanoyl vanillylamide-4-glyceryl ether, N-(4-O-acetic acid sodium)-3-methoxybenzyl-nonamide (sodium N-nonanoyl vanillylamide-4-O-acetate), N-(4-O-glycol-3-methoxybenzyl)-nonamide (N-nonanoyl vanillylamide-4-glycol ether), 20-homovanillyl-mezerein, 20-homovanillyl-12-deoxyphorbol-13-phenylacetate), civamide (N-[(4-hydroxy-3-methoxyphenyl)-methyl]-8-methyl-(Z)-6-nonemamide), nuvanil, capsavanil, olvanil, arvanil, and palvanil (N-palmitoyl-vanillamide).

In some embodiments of the disclosure, the TRPA1 channel activator is allyl isothiocyanate, a gingerol, cinnamaldehyde, acrolein, farnesyl thiosalicylic acid, Δ_9-tetrahydrocannabinol, eugenol, a shogaol, a sanshool, allicin, diallyl sulfide, diallyl disulfide, diallyl trisulfide, or farnesyl thioacetic acid. In some embodiments, the TRPA1 channel activator is present from about 0.001% to about 10% (w/w) or from about 0.001% to about 10% (v/v).

In some embodiments, the ASIC channel activator comprises acetic acid, phosphoric acid, citric acid, malic acid, succinic acid, lactic acid, tartaric acid, fumaric acid, or ascorbic acid. In some embodiments, the ASIC channel activator is present from about 0.001% to about 10% (w/w) or from about 0.001% to about 10% (v/v).

In some embodiments, the composition is formulated as a liquid or a solid. In some embodiments, the composition is formulated as a liquid. In some embodiments, the liquid is selected from the group consisting of emulsions, microemulsions, solutions, suspensions, syrups (*e.g.*, syrup concentrates), linctuses, drops, sprays, and elixirs. In some embodiments, the composition is formulated as a solid. In some embodiments, the solid is selected from the group consisting of tablets, capsules, powders, crystals, pastes, gels, lozenges (*e.g.*, liquid filled lozenges), gums, candies, chews, foodstuffs, dissolving strips, films, and semi-solid formulations. In some embodiments, said solid is a tablet or capsule. In some embodiments, said capsule is a hard or soft capsule.

In another aspect, the present disclosure relates to the use of a composition comprising an ion channel activator in the manufacture of a medicament, for treating a subject for unwanted or abnormal muscle contraction or absence of a normal muscle contraction; wherein knowledge of a

result of a test for the efficacy of the administration of a test aliquot of said composition for alleviation of test muscle contraction in said subject has been acquired; and wherein the medicament is to be administered in an amount sufficient to alleviate unwanted or abnormal muscle contraction or absence of a normal muscle contraction to said subject. In an embodiment, the disclosure features a method of treating a subject for unwanted or abnormal muscle contraction (*e.g.*, cramp, spasm, dystonia, or fasciculation) or absence of a normal muscle contraction (*e.g.*, gait abnormalities, *e.g.*, foot drop) comprising: acquiring, *e.g.*,

directly or indirectly, knowledge of a result of a test for the efficacy of the administration of a test aliquot of a composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) for alleviation of test muscle contraction in said subject; and administering, *e.g.*, in response to said result, an amount of a composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) sufficient to alleviate unwanted or abnormal muscle contraction or absence of normal muscle contraction to said subject. In some embodiments, the test comprises directly acquiring said knowledge. In some embodiments, the test comprises further performing said test.

In some embodiments, said muscle contraction comprises a muscle cramp. In some embodiments, said muscle contraction comprises a muscle spasm. In some embodiments, said muscle contraction comprises a dystonia. In some embodiments, said muscle contraction comprises a fasciculation. In some embodiments, said muscle contraction occurs in a skeletal muscle. In some embodiments, said muscle contraction occurs in a smooth muscle. In some embodiments, the test muscle contraction is a test muscle cramp or a test muscle spasm.

In some embodiments, said composition comprises a plurality of (*e.g.*, two or three) ion channel activators (*e.g.*, TRPV1 channel activators, TRPA1 channel activators, ASIC channel activators, or combinations thereof). In some embodiments, said composition further comprises a pharmaceutically acceptable excipient. In some embodiments, said composition comprises an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof), and a plurality of pharmaceutically acceptable excipients.

In some embodiments, the TRPV1 channel activator is a capsaicinoid, a capsinoid, oleoylethanolamide, N-oleoyldopamine, 3-methyl-N-oleoyldopamine, oleamide, capsiate, a 1-monoacylglycerol having C18 and C20 unsaturated and C8-C12 saturated fatty acid, a 2-monoacylglycerol having C18 and C20 unsaturated fatty acids, miogadial, miogatrial, polygodial, a terpenoid with an alpha,beta-unsaturated 1,4-dialdehyde moiety, sanshool, evodiamine, acesulfame-K, cyclamate, $CuSO_4$, $ZnSO_4$, $FeSO_4$, arvanil, anandamide, N-arachidonoyl-dopamine, flufenamic acid dopamide, a dopamine amide of fenamic acid, 4-hydroxynonenal, 1-[2-(1-adamantyl)ethyl]-1-pentyl-3-[3-(4-pyridyl)propyl]urea, or gingerol.

In particular embodiments, the capsaicinoid is capsaicin. In some

embodiments, the TRPV1 channel activator is present from about 0.001% to about 10% (w/w) or from about 0.001% to about 10% (v/v).

In some embodiments, the TRPV1 channel activator is naturally occurring or non-naturally occurring. In some embodiments, said naturally occurring TRPV1 channel activator is selected from the group consisting of: capsaicin, dihydrocapsaicin, nordihydrocapsaicin, homodihydrocapsaicin, homocapsaicin, nonivamide, pseudocapsaicin, resiniferatoxin, tinyatoxin, capsiate, dihydrocapsiate, nordihydrocapsiate, norcapsaicin, capsiconiate, dihydrocapsiconiate and other coniferyl esters, capsiconinoid, and 3-hydroxyacetanilide.

In some embodiments, the non-naturally occurring TRPV1 channel is selected from the group consisting of: 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl formate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl acetate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl propanoate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl butanoate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methoxyphenyl 2,2-dimethylpropanoate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl octadecanoate, 4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methyoxyphenyl{4-[((6E)-8-methylnon-6-enoylamino)methyl]-2-methoxyphenoxy}formate, homovanillyl 8-methylnonanoate, 3-(3-methoxy-4-hydroxyphenyl)propyl 8-methylnonanoate, 8-methylnonyl homovanillate, 8-methylnonanoic acid-substituted benzyl ester derivative, heptanoyl isobutylamide, heptanoyl guaiacylamide, 7-phenylhept-6-yne-acid-4-hydroxy-3-methoxybenzylamide, dohevanil, denatonium capsaicinate, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(4-chlorophenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(4-fluorophenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(2,4-dichlorophenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(4-benzyloxyphenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[2-(4-(N-octyloxy)phenyl)ethyl]thiourea, N-[4-(2-aminoethoxy)-3-methoxybenzyl]-N'-[4-N-octyloxybenzyl]thiourea, N-phenylmethylalkynamide capsaicin derivatives, N-(4-O-glycerol-3-methoxybenzyl)nonamide, N-nonanoyl vanillylamide-4-glyceryl ether, N-(4-O-acetic acid sodium)-3-methoxybenzyl-nonamide (sodium N-nonanoyl vanillylamide-4-O-acetate), N-(4-o-glycol-3-methoxybenzyl)-nonamide (N-nonanoyl vanillylamide-4-glycol ether), 20-homovanillyl-mezerein, 20-homovanillyl-12-deoxyphorbol-13-

phenylacetate), civamide (N-[(4-hydroxy-3-methoxyphenyl)-methyl]-8-methyl-(Z)-6-nonemamide), nuvanil, capsavanil, olvanil, arvanil, and palvanil (N-palmitoyl-vanillamide).

In some embodiments of the disclosure, the TRPA1 channel activator is allyl isothiocyanate, a gingerol, cinnamaldehyde, acrolein, farnesyl thiosalicylic acid, Δ_9-tetrahydrocannabinol, eugenol, a shogaol, a sanshool, allicin, diallyl sulfide, diallyl disulfide, diallyl trisulfide, or farnesyl thioacetic acid. In some embodiments, the TRPA1 channel activator is present from about 0.001% to about 10% (w/w) or from about 0.001% to about 10% (v/v).

In some embodiments, the ASIC channel activator comprises acetic acid, phosphoric acid, citric acid, malic acid, succinic acid, lactic acid, tartaric acid, fumaric acid, or ascorbic acid. In some embodiments, the ASIC channel activator is present from about 0.001% to about 10% (w/w) or from about 0.001% to about 10% (v/v).

In some embodiments, the subject has a central nervous system disorder or injury, *e.g.*, a brain injury, stroke, or traumatic spinal cord injury. In some embodiments, the subject has been diagnosed with or identified as having multiple sclerosis. In some embodiments, the subject has been diagnosed with or identified as having dystonia, *e.g.*, cervical dystonia. In some embodiments, the subject has been diagnosed with or identified as having spinal cord spasticity. In some embodiments, said subject has been diagnosed with or identified as having a disorder associated with muscle cramps, *e.g.*, any of the disorders disclosed herein, *e.g.*, night cramps, multiple sclerosis, spinal cord spasticity, or dystonia.

In some embodiments, said muscle contraction being selected, treated, or diagnosed, comprises a contraction in a muscle other than a muscle that is contracted in the test muscle contraction. In some embodiments, said test muscle contraction comprises a contraction in a muscle of the foot, *e.g.*, the flexor hallucis brevis muscle, and the muscle cramp comprises a cramp in a muscle other than the foot, *e.g.*, the flexor hallucis brevis muscle. In some embodiments, said muscle contraction is not induced by applied electrical stimulation.

In some embodiments, said muscle contraction is a night cramp. In some embodiments, said muscle contraction is associated with multiple sclerosis. In some embodiments, said muscle contraction is associated with spinal cord spasticity. In some embodiments, said muscle contraction is associated with dystonia.

some embodiments, the composition is formulated as a solid. In some embodiments, the solid is selected from the group consisting of tablets, capsules, powders, crystals, pastes, gels, lozenges (*e.g.*, liquid filled lozenges), gums, candies, chews, foodstuffs, dissolving strips, films, and semi-solid formulations. In some embodiments, said solid is a tablet or capsule. In some embodiments, said capsule is a hard or soft capsule.

In another embodiment, the disclosure features a method of evaluating a subject for abnormal or unwanted muscle contraction or absence of normal muscle contraction comprising: acquiring, *e.g.*, indirectly or directly, knowledge of a result of a test for the efficacy of the administration of a test aliquot of a composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) for alleviation of test muscle contraction in said subject; and responsive to said result, classifying said subject. In some embodiments, said subject has been diagnosed or identified as having a disorder associated with muscle cramps, *e.g.*, any of the disorders disclosed herein, *e.g.*, night cramps, multiple sclerosis, spinal cord spasticity, or dystonia. In some embodiments, the test comprises directly acquiring said knowledge. In some embodiments, the test further comprises performing said test.

In some embodiments, said result is indicative of a preselected level of alleviation of the test muscle contraction by administration of the test aliquot. In some embodiments, said result is indicative of the alleviation of the test muscle contraction by administration of the test aliquot.

In some embodiments, the test comprises classifying said subject as a candidate for treatment with a composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof). In some embodiments, said result is indicative of the failure to provide a preselected level of alleviation of the test muscle contraction by administration of the test aliquot. In some embodiments, said result is indicative of the absences of alleviation of the test muscle contraction by administration of the test aliquot. In some embodiments, the test comprises classifying said subject as not being a candidate for treatment with a composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC

channel activator, or combination thereof). In some embodiments, said method is computer implemented.

In some embodiments, said composition comprises a plurality of (*e.g.*, two or three) ion channel activators (*e.g.*, TRPV1 channel activators, TRPA1 channel activators, ASIC channel activators, or combinations thereof). In some embodiments, said composition further comprises a pharmaceutically acceptable excipient. In some embodiments, said composition comprises an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof), and a plurality of pharmaceutically acceptable excipients.

In another embodiment, the disclosure features a computer-implemented method of evaluating a subject for unwanted or abnormal muscle contraction, *e.g.*, cramp, spasm, dystonia, or fasciculation or absence of a normal muscle contraction, *e.g.*, gait abnormalities, *e.g.*, foot drop comprising: a) acquiring, *e.g.*, directly or indirectly, a value for a parameter related to the effect of administering a test aliquot of a composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof) on test muscle cramping, *e.g.*, by evaluating the electrical activity of said test muscle, *e.g.*, by EMG; b) evaluating the effectiveness of administering the test aliquot on a computer, *e.g.*, by comparing a test value or profile with a treatment value or profile; c) responsive to the evaluation, comprising classifying said subject as a candidate for treatment with a composition comprising a capsaicinoid, capsinoid, or related analog or combination thereof.

In some embodiments, said composition comprises a plurality of (*e.g.*, two or three) ion channel activators (*e.g.*, TRPV1 channel activators, TRPA1 channel activators, ASIC channel activators, or combinations thereof). In some embodiments, said composition further comprises a pharmaceutically acceptable excipient. In some embodiments, said composition comprises an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof), and a plurality of pharmaceutically acceptable excipients.

In some embodiments, the composition is formulated as a liquid or a solid. In some embodiments, the liquid is selected from the group consisting of emulsions, microemulsions,

solutions, suspensions, syrups (*e.g.*, syrup concentrates), linctuses, drops, sprays, and elixirs. In some embodiments, the composition is formulated as a solid. In some embodiments, the solid is selected from the group consisting of tablets, capsules, powders, crystals, pastes, gels, lozenges (*e.g.*, liquid filled lozenges), gums, candies, chews, foodstuffs, dissolving strips, films, and semi-solid formulations. In some embodiments, said solid is a tablet or capsule. In some embodiments, said capsule is a hard or soft capsule.

In another embodiment, the disclosure features a system comprising a memory; and a processing unit operative to: a) evaluate the effectiveness of administering a test aliquot of a composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof); b) responsive to the evaluation, comprising classifying said subject as a candidate for treatment with a composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof).

In another embodiment, the disclosure features a computer-readable medium comprising computer-executable instructions that, when executed on a processor of a computer, perform a method comprising acts of: a) evaluating the effectiveness of administering a test aliquot of a composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof); b) responsive to the evaluation, comprising classifying said subject as a candidate for treatment with a composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof).

In some embodiments, said subject has been diagnosed or identified as having a disorder associated with muscle cramps, spasms, dystonia, or fasciculations, *e.g.*, any of the disorders disclosed herein, *e.g.*, night cramps, multiple sclerosis, spinal cord spasticity, or dystonia.

In another embodiment, the disclosure features a kit comprising a liquid tight container comprising one or more of: one or a plurality of test aliquots of a composition comprising an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof); one or a plurality of leads for conducting current to a subject

and inducing a cramp; and one or a plurality of leads for measuring electrical activity associated with a cramp. In some embodiments, said kit further comprises a plurality, *e.g.*, at least 2, 3, 4, 5, 6, 7, 8, 9, or 10, test aliquots of the composition.

In some embodiments, said test aliquot of the composition comprises a plurality of (*e.g.*, two or three) ion channel activators (*e.g.*, TRPV1 channel activators, TRPA1 channel activators, ASIC channel activators, or combinations thereof). In some embodiments, said test aliquot of the composition further comprises a pharmaceutically acceptable excipient. In some embodiments, said test aliquot of the composition comprises an ion channel activator (*e.g.*, a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or combination thereof), and a plurality of pharmaceutically acceptable excipients.

In some embodiments, said test aliquot of the composition comprises a TRP channel activator or an ASIC channel activator. In some embodiments, said TRP channel activator comprises a TRPV1 activator and a TRPA1 activator. In some embodiments, said composition comprises a TRP activator and an ASIC channel activator. In certain embodiments, the TRPV1 agonist is a capsaicinoid, *e.g.*, capsaicin. In some embodiments, the TRPV1 channel activated by said ion channel activator (e.g., a TRPV1 channel activator, TRPA1 channel activator, ASIC channel activator or combination thereof) is present on a sensory neuron in the mouth, the esophagus and/or the stomach. In some embodiments, said ion channel activator (e.g., a TRPV1 channel activator, TRPA1 channel activator, ASIC channel activator or combination thereof) increases inhibitory signaling to alpha motor neurons.

In some embodiments, the composition is formulated as a liquid or a solid. In some embodiments, the liquid is selected from the group consisting of emulsions, microemulsions, solutions, suspensions, syrups (*e.g.*, syrup concentrates), linctuses, drops, sprays, and elixirs. In some embodiments, the composition is formulated as a solid. In some embodiments, the solid is selected from the group consisting of tablets, capsules, powders, crystals, pastes, gels, lozenges (*e.g.*, liquid filled lozenges), gums, candies, chews, foodstuffs, dissolving strips, films, and semi-solid formulations. In some embodiments, said solid is a tablet or capsule. In some embodiments, said capsule is a hard or soft capsule.

In another embodiment, the disclosure features a method of evaluating a composition for treating unwanted or abnormal muscle contraction, *e.g.*, cramp, spasm, dystonia, or fasciculation,

48. The composition of any one of claims 27-47, wherein said ion channel activator is to be ingested by the subject.

49. The composition of any one of claims 27-48, wherein said ion channel activator is to be held in the mouth by the subject.

50. The composition of any one of claims 27-49, wherein said ion channel activator is to be dissolved in the mouth of the subject or chewed by the subject prior to swallowing.

51. Use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient in the manufacture of a medicament, for treating a painful muscle contraction in a subject in need thereof.

52. The use of claim 51, wherein said painful muscle contraction is a muscle contraction of the head or neck.

53. The use of any one of claims 51-52, wherein said painful muscle contraction is associated with tension headache, cluster headache, or migraine headache.

54. Use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient in the manufacture of a medicament, for treating tactile sensitivity in a subject in need thereof.

55. The use of claim 54, wherein said tactile sensitivity is associated with autism, dyspraxia, neuralgia, anxiety disorders, venomous bites, or venomous stings.

56. The use of claim 55, wherein said anxiety disorder is selected from the group consisting of panic disorder, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), social anxiety disorder, phobia, and generalized anxiety disorder (GAD).

57. Use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient in the manufacture of a medicament, for treating a dystonia in a subject in need thereof.

58. The use of claim 57, wherein said dystonia is selected from the group consisting of: focal dystonia, blepharospasm, cervical dystonia, cranial dystonia, laryngeal dystonia, and hand dystonia.

59. Use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient in the manufacture of a medicament, for treating a peripheral nervous system (PNS) condition in a subject in need thereof.

60. The use of claim 59, wherein said PNS condition is selected from the group consisting of: cramp fasciculation syndrome, Isaacs' Syndrome or neuromyotonia, peripheral neuropathy, carpal tunnel syndrome, and Epstein-Barr virus infection.

61. Use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient in the manufacture of a medicament, for treating a throat condition in a subject in need thereof.

62. The use of claim 61, wherein said throat condition is associated with chemical injury, cancer, surgical injury, or pathogen infection.

63. The use of any one of claims 61-62, wherein said throat condition is selected from the group consisting of: acid reflux, laryngospasm, dysphagia, and spasmodic dysphonias.

64. Use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient in the manufacture of a medicament, for treating a condition associated with an electrolyte imbalance or vitamin deficiency in a subject in need thereof.

65. The use of claim 64, wherein said condition is selected from the group consisting of: hyponatremia, hypocalcemia, hypomagnesemia, kidney disease, rickets, calcium or magnesium deficiency, thiamine deficiency, hypoparathyroidism, medullary cystic disease, and adrenocortical carcinoma.

66. Use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient in the manufacture of a medicament, for treating a central nervous system (CNS) condition in a subject in need thereof.

67. The use of claim 68, wherein said CNS condition is associated with a tumor.

68. The use of any one of claims 66-67, wherein said CNS condition is selected from the group consisting of: multiple sclerosis, cerebral palsy, stroke, motor neuron disease, spinal injury, and stenosis.

69. Use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient in the manufacture of a medicament, for treating a muscle condition or disorder in a subject in need thereof.

70. The use of claim 69, wherein said muscle condition or disorder is associated with muscle pain, muscle spasms, muscle cramps, fasciculations, or any combination thereof.

71. The use of any one of claims 69-70, wherein said muscle condition or disorder is a neuromuscular disorder.

72. The use of any one of claims 69-71, wherein said muscle condition or disorder is muscle pain, muscle spasms, spasticity, or fasciculations associated with motor neuron disease.

73. The use of claim 72, wherein said motor neuron disease is selected from the group consisting of amyotrophic lateral sclerosis, primary lateral sclerosis, progressive muscular

atrophy, progressive bulbar palsy, pseudobulbar palsy, spinal muscular atrophy, progressive spinobulbar muscular atrophy, and post-polio syndrome.

74. The use of any one of claims 69-73, wherein said muscle condition or disorder is associated with treatment of said subject with dialysis, diuretics, β-blockers, statins, fibrates, β2-agonists, ACE inhibitors, ARBs, anti-psychotic medications, or any combination thereof.

75. The use of claim 74, wherein said muscle condition or disorder is associated with treatment of said subject with statins and fibrates.

76. The use of any one of claims 69-75, wherein said muscle condition or disorder occurs in one or more skeletal muscles.

77. The use of any one of claims 69-76, wherein said muscle condition or disorder is refractory to an approved treatment.

78. The use of claim 77, wherein said approved treatment is botox, cyclopenzaprine, orphenadrine, baclofen, or any combination thereof.

79. The use of any one of claims 69-78, wherein said muscle condition or disorder involves muscle claudication pain.

80. The use of claim 79, wherein said muscle claudication pain is associated with inactivity, restriction, economy class syndrome, paralysis, peripheral artery disease, or immobilization.

81. Use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient in the manufacture of a medicament, for treating a respiratory condition in a subject in need thereof.

82. The use of claim 78, wherein said respiratory condition comprises asthma, chronic obstructive pulmonary disease, bronchitis, emphysema, pneumonia, cystic fibrosis, pleural cavity diseases, influenza, or cold.

83. Use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient in the manufacture of a medicament, for treating cough in a subject in need thereof.

84. The use of claim 83, wherein said cough is caused by a respiratory condition, exposure to allergens or chemical irritants, or inflammation.

85. Use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient in the manufacture of a medicament, for treating sarcoidosis in a subject in need thereof.

86. Use of a composition comprising an effective amount of an ion channel activator and a pharmaceutically acceptable excipient in the manufacture of a medicament, for treating a connective tissue disease in a subject in need thereof.

87. The use of claim 86, wherein said connective tissue disease is selected from the group consisting of Ehlers-Danlos syndrome, epidermolysis bullosa, Marfan syndrome, osteogenesis imperfect, arthritis, scleroderma, Sjögren's syndrome, lupus, vasculitis, mixed connective tissue disease, cellulitis, polymyositis, and dermatomyositis.

88. The use of claim 87, wherein said arthritis is rheumatoid arthritis, osteoarthritis, gout, or psioratic arthritis, or wherein said vasculitis is Wegener's granulomatosis or Churg-Strauss Syndrome.

89. The use of any one of claims 51-88, wherein said TRPV1 channel activator is a capsaicinoid, a capsinoid, oleoylethanolamide, N-oleoyldopamine, 3-methyl-N-oleoyldopamine, oleamide, capsiate, a 1-monoacylglycerol having C18 and C20 unsaturated and C8-C12 saturated

fatty acid, a 2- monoacylglycerol having C18 and C20 unsaturated fatty acids, miogadial, miogatrial, polygodial, a terpenoid with an alpha,beta-unsaturated 1,4-dialdehyde moiety, sanshool, evodiamine, acesulfame-K, cyclamate, $CuSO_4$, $ZnSO_4$, $FeSO_4$, arvanil, anandamide, N-arachidonoyl-dopamine, flufenamic acid dopamide, a dopamine amide of fenamic acid, 4-hydroxynonenal, 1-[2-(1-adamantyl)ethyl]-1-pentyl-3-[3-(4-pyridyl)propyl]urea, or gingerol.

90. The use of any one of claims 51-88, wherein said TRPA1 channel activator is allyl isothiocyanate, gingerol, cinnamaldehyde, acrolein, farnesyl thiosalicylic acid, Δ_9-tetrahydrocannabinol, eugenol, a shogaol, a sanshool, allicin, diallyl sulfide, diallyl disulfide, diallyl trisulfide, or farnesyl thioacetic acid.

91. The use of any one of claims 51-88, wherein said ASIC channel activator comprises acetic acid, phosphoric acid, citric acid, malic acid, succinic acid, lactic acid, tartaric acid, fumaric acid, or ascorbic acid.

92. The use of any one of claims 51-88, wherein said composition is formulated as a liquid.

93. The use of claim 93, wherein said liquid is selected from the group consisting of emulsions, microemulsions, solutions, suspensions, syrups, linctuses, drops, sprays, and elixirs.

94 The use of any one of claims 51-88, wherein said composition is formulated as a solid.

95. The use of claim 94, wherein said solid is selected from the group consisting of tablets, capsules, powders, crystals, pastes, gels, lozenges, gums, candies, chews, foodstuffs, dissolving strips, films, and semi-solid formulations.

96. The use of claim 95, wherein said capsule is a hard or soft capsule.

97. Use of a composition comprising an ion channel activator in the manufacture of a medicament, for treating a subject for unwanted or abnormal muscle contraction or absence of a normal muscle contraction;

wherein knowledge of a result of a test for the efficacy of the administration of a test aliquot of said composition for alleviation of test muscle contraction in said subject has been acquired; and

wherein the medicament is to be administered in an amount sufficient to alleviate unwanted or abnormal muscle contraction or absence of a normal muscle contraction to said subject.

98. The use of claim 97, wherein said muscle contraction comprises a muscle cramp, muscle spasm, dystonia, or fasciculation.

99. The use of any one of claims 97-98, wherein said muscle contraction occurs in a skeletal muscle or smooth muscle.

100. The use of claim 97, wherein the test muscle contraction is a test muscle cramp or a test muscle spasm.

101. The use of claim 97, wherein the subject has a central nervous system disorder or injury.

102. The use of claim 97, wherein the subject has been diagnosed with or identified as having multiple sclerosis.

103. The use of claim 97, wherein the subject has been diagnosed with or identified as having dystonia.

104. The use of claim 97, wherein the subject has been diagnosed with or identified as having spinal cord spasticity.

105. The use of claim 97, wherein said subject has been diagnosed with or identified as having a disorder associated with muscle cramps, muscle pain, muscle spasms, spasticity, or fasciculations.

106. The use of claim 97, comprising directly acquiring said knowledge.

107. The use of claim 97, wherein said muscle contraction being selected, treated, or diagnosed comprises a contraction in a muscle other than a muscle that is contracted in the test muscle contraction.

108. The use of claim 97, wherein said test muscle contraction comprises a contraction in a muscle of the foot and the muscle cramp comprises a cramp in a muscle other than the foot.

109. The use of claim 97, wherein said muscle contraction is not induced by applied electrical stimulation.

110. The use of claim 97, wherein said muscle contraction is a night cramp.

111. The use of claim 97, wherein said muscle contraction is associated with multiple sclerosis.

112. The use of claim 97, wherein said muscle contraction is associated with spinal cord spasticity.

113. The use of claim 97, wherein said muscle contraction is associated with dystonia.

114. The use of claim 97, wherein said test muscle contraction was induced by application of electrical stimulation.

115. The use of claim 97, wherein it has been determined that a muscle contraction can be induced in the subject by application of electrical stimulation.

116. The use of claim 97, wherein said knowledge is acquired by: evaluating the effect of the test aliquot of the composition which has been administered to said subject on an induced test muscle contraction.

117. The use of any one of claims 97-116, wherein said ion channel activator comprises a TRPV1 channel activator, a TRPA1 channel activator, an ASIC channel activator, or a combination thereof.

118. The use of claim 117, wherein said TRPV1 channel activator is a capsaicinoid, a capsinoid, oleoylethanolamide, N-oleoyldopamine, 3-methyl-N-oleoyldopamine, oleamide, capsiate, a 1-monoacylglycerol having C18 and C20 unsaturated and C8-C12 saturated fatty acid, a 2- monoacylglycerol having C18 and C20 unsaturated fatty acids, miogadial, miogatrial, polygodial, a terpenoid with an alpha,beta-unsaturated 1,4-dialdehyde moiety, sanshool, evodiamine, acesulfame-K, cyclamate, $CuSO_4$, $ZnSO_4$, $FeSO_4$, arvanil, anandamide, N-arachidonoyl-dopamine, flufenamic acid dopamide, a dopamine amide of fenamic acid, 4-hydroxynonenal, 1-[2-(1-adamantyl)ethyl]-1-pentyl-3-[3-(4-pyridyl)propyl]urea, or gingerol.

119. The use of claim 117, wherein said TRPA1 channel activator is allyl isothiocyanate, a gingerol, cinnamaldehyde, acrolein, farnesyl thiosalicylic acid, Δ_9-

tetrahydrocannabinol, eugenol, a shogaol, a sanshool, allicin, diallyl sulfide, diallyl disulfide, diallyl trisulfide, or farnesyl thioacetic acid.

120. The use of claim 117, wherein said ASIC channel activator comprises acetic acid, phosphoric acid, citric acid, malic acid, succinic acid, lactic acid, tartaric acid, fumaric acid, or ascorbic acid.

121. The use of claim 117, wherein said TRPV1 channel activator, TRPA1 channel activator, ASIC channel activator, or combination thereof is present from about 0.001% to about 10% (w/w) or about 0.001% to about 10% (v/v).