Bipolar disorder is known to be a group of affective disorders depicted by depressive manic or hypomanic disorders. Indeed, considered as an oldie as its pharmaceutical usage started in the 19th-century, lithium is also a goodie used as the first-line treatment for bipolar disorder, also it is considered to be the only treatment with anti-suicidal effects. During treatment, lithium levels should be monitored as its therapeutic levels (0.5–0.8 mM) in the blood are close to intoxication levels (>1.5 mM) and to severe intoxication levels >2.5 mM that might induce coma. That is why it is necessary for patients diagnosed with bipolar disorder to monitor lithium levels frequently. In fact, there are many traditional analytical techniques for lithium detection. Still, these are associated with limitations as they are very expensive, time-consuming, and not found in all laboratories. So, the need to develop a cost-effective, sensitive, and easy-to-handle devices has grown. Affinity sensors constituted a promising potential for the sensitive detection of lithium. This review, to my knowledge, is the first review highlighting the different types of biosensors developed for lithium-ion detection while explaining the mode of action of each biosensor, and talking about all possible biological fluids that can be used for the detection of this drug.

© 2022 The Author(s). Published on behalf of The Electrochemical Society by IOP Publishing Limited. This is an open access article distributed under the terms of the Creative Commons Attribution 4.0 License (CC BY, http://creativecommons.org/licenses/by/4.0/), which permits unrestricted reuse of the work in any medium, provided the original work is properly cited. [DOI: 10.1149/2754-2734/ac8065]
II. The universality of hypomania is 2.6 to 7.8%, and about 0.5%–6.3% for Cyclothymia.\textsuperscript{16}

Most studies show an equal rate of BD type I between men and women,\textsuperscript{17} while some demonstrate a higher rate of manic periods in men and higher prevalence rates of BD type II in women.\textsuperscript{16} In general, the proof isn’t solid to move from the perspective that bipolar seems to have roughly equivalent dissemination across sex and nationality.

The average age of the beginning of BD is mid-twenties,\textsuperscript{16} in spite of the fact that discoveries fluctuate between 20–30 years.\textsuperscript{18}

The bimodal dissemination was proposed\textsuperscript{19} based on a large cohort study established that at the age of 15 to 24 and 45 to 54 years old peaks in BD.\textsuperscript{20} It is vital that the time of beginning is hard to study established that at the age of 15 to 24 and 45 to 54 years old bipolar seems to have roughly equivalent dissemination across sex and nationality.

During the treatment, renal functions shall be tested every 6 months especially levels of urea and creatinine.\textsuperscript{26} Patients to give a blood sample in order to monitor serum lithium status.

Therefore, it is important that physicians monitor lithium serum levels in order to prevent intoxication.

Current analytical methods for lithium-ion detection and their limitations.—Currently, there are several developed analytical methods for the detection of lithium like flame emission photometry and atomic absorption spectroscopy.\textsuperscript{31} both are not present in most hospitals and laboratories which makes lithium frequent monitoring impossible, and capillary electrophoresis which requires a pre-concentrate, is very expensive and requires a trained personnel.\textsuperscript{32} X-ray fluorescence spectrometry that is not designed to detect light elements such as lithium which limits its usage. Also, they are only suitable for quantitative analysis, as they must be coupled with other chromatographic techniques that could lead to a risk in the sample change in storage or handling.\textsuperscript{32}

The limitations of the currently developed analytical techniques will be summarized in Fig. 1.

Composition of the biological fluids.—Known as the quintessence of life, humans are composed fundamentally of water, the aqueous solution in which all necessary biochemical reactions happen to produce life. In addition, fluids can be divided into two categories the intracellular: rich in phosphate, magnesium, potassium, and proteins, but lower in sodium, chloride, and bicarbonate, and the extracellular fluids that are rich in sodium, chloride, bicarbonate, and proteins but lower in magnesium, potassium, and phosphate even though the chemical composition between humans varies inside the biological fluids.\textsuperscript{33}

Blood.—Blood has a role in maintaining the hemostasis of all cells in the body this is acquired by the exchange phenomenon of cellular debris with nutrients from the digestive and respiratory systems. This makes the blood rich in nutrients and cellular contents\textsuperscript{34} and a perfect medium for monitoring humans’ health status.

All present analytical techniques for lithium-ion detection require patients to give a blood sample in order to monitor serum lithium levels frequently and prevent toxicity.

Saliva.—Salivary glands produce saliva. The daily flow average is between 1 and 1.5 l of saliva production. Saliva is first secreted by acinar cells that determine the type of saliva produced from the different glands.\textsuperscript{35} Saliva is composed of 98% water and electrolytes (sodium, potassium, lithium, etc.).\textsuperscript{36} mucus (glycoproteins), enzymes (amylase),\textsuperscript{37} and antimicrobial agents (IgA).\textsuperscript{38}

As regards its use as a diagnostic medium, saliva shows many advantages over the blood, starting with its collection which is less stressful, as it is non-invasive compared to the blood, and it is a preferred medium for patients diagnosed with BD as they have to frequently monitor lithium therapeutic levels.

| Table I. Suggested medical examinations for lithium monitoring. |
|---------------------------------------------------------------|
| **SUGGESTED MEDICAL EXAMINATION TESTS**                      |
| **TIME**                                                     |
| RENAL FUNCTION                                             | Before the start, every 6 months |
| CALCIUM                                                     | At the start, every 6 months, annually |
| THYROID FUNCTION                                           | At the start, every 6 months, annually |
| ELECTROCARDIOGRAM: RISK OF QTC INTERVAL PROLONGATION        | |

Guidelines to Initiate and Maintain Lithium Treatment

Before the initiation of Lithium treatment, it is important to take into consideration several indispensable factors. To start, excretion of lithium is via the kidneys, thus renal functions must be checked as a reduced renal function will result in the accumulation of lithium in the kidneys and conclusively toxicity.\textsuperscript{25} During the treatment, renal functions shall be tested every 6 months’ especially levels of urea and creatinine.\textsuperscript{26}

Secondly, it is recommended to check the thyroid functions annually as lithium acts on thyroid-stimulating hormone, thyroxine, and triiodothyronine.\textsuperscript{27}

Thirdly, studies showed the prevalence of hyperparathyroidism being 7.5% more in patients on lithium treatment than in the general population, thus the need to monitor Calcium serum levels.\textsuperscript{28} Suggested medical examinations for safety purposes during lithium treatment are presented in Table I.

Adding to these side effects that sometimes occur within lithium therapeutic levels, lithium serum levels should be monitored as the therapeutic levels 0.5 to 0.8 mM are close to the intoxication levels. Plasma levels of 1.2 mM can be potentially toxic, whereas levels that exceed 2 mM can be fatal.\textsuperscript{29}

Lithium intoxication can affect the central nervous system, the kidneys, the intestine, and the cardiovascular system. Central nervous system symptoms range from confusion to polyneuropathy. Gastrointestinal symptoms include nausea, vomiting, and diarrhea. Renal symptoms include polyuria and diabetes insipidus. Cardiovascular signs like low blood pressure and rarely shock.\textsuperscript{30}

Table I. Suggested medical examinations for lithium monitoring.
Unlike blood testing which searches for compounds that are mostly protein-bound traveling through the blood serum, the saliva looks at the cellular levels that correspond to a representation of what’s clinically relevant. Unbound hormones that are indicators of health and disease in humans can be detected in saliva as well as small molecules that travel freely through the cells and into the saliva ducts. Salivary samples can be analyzed for tissue fluid levels of naturally, therapeutically, and recreationally introduced substances, patient hormonal status, immunologic status, and neurologic status. Thus, monitoring lithium levels can be done in blood as well as saliva noting that lithium levels in the saliva are 2/3 times higher than that of the blood, with the effective therapeutic range of lithium being 1.5 to 2.5 mM.2

Saliva testing can thus be safer, faster, and more economical than blood testing.

Saliva samples can be analyzed for tissue fluid levels of naturally, therapeutically, and recreationally introduced substances, patient hormonal status, immunologic status, and neurologic status. Thus, monitoring lithium levels can be done in blood, as well as saliva noting that lithium levels in the saliva are 2/3 times higher than that of the blood, with the effective therapeutic range of lithium being 1.5 to 2.5 nM.2

Saliva testing can thus be safer, faster, and more economical than blood testing.

Table II. Characteristics of the samples.6

|                         | n  | %  |
|-------------------------|----|----|
| Total sample            | 50 | 100|
| Female gender           | 27 | 54 |
| BD type 1               | 46 | 92 |
| BD type 2               | 4  | 8  |
| Treatment Lithium       | 38 | 76 |
| Treatment VPA           | 12 | 24 |
| **Mean**                |    |    |
| Age                     | 43.2| 16.34|
| Lithium serum concentration | 0.72| 0.22 |
| Lithium salivary concentration | 2.04| 0.74 |
| Serum VPA concentration  | 75.78| 18.98 |
| Salivary VPA concentration | 0.84| 0.57 |

Notes: BD = Bipolar Disorder; SD = Standard Deviation; Li = lithium; VPA = valproate.

However, the fact that the metabolites are present in low quantities and vary from one patient to another limits its usage.41

In addition, studies showed that it is very hard to maintain the accuracy of the results, as many factors affect the accurate concentration as some food consumption and the time of the sample’s collection.

A Correlation between Salivary and serum Li levels in Patient diagnosed with BD.

As previously mentioned, lithium has a narrow therapeutic window, thus its levels need to be regularly checked.

It is well known that approximately 3 to 4.5% of the general population have a needle fear, adding to those patients with chronic illnesses (diabetes, multiple sclerosis). This fact has developed a treatment resistance for some patients, especially when it requires a lot of blood testing.42

A recent study showed a good linear correlation between lithium serum levels and salivary levels in patients (different age, gender, and BD type) diagnosed with BD, with lithium concentration being higher in the saliva than in serum, this study also found the lack of correlation between serum and salivary levels of valproate, another first-line treatment for BD.6

This could open a door to the routine clinical use of salivary measurements for patients on Lithium treatment as they could benefit from simple, cost-effective, rapid, and accurate salivary measurements. The main advantage of these tests is that it is a non-invasive method.6

Table II shows the characteristics of the samples and the mean of serum and saliva Lithium concentrations.

**Affinity Sensors**

As previously mentioned, there are several analytical techniques for metal detection, but these techniques are associated with limitations. Recently, the use of affinity sensors for the detection of heavy metal ions (HMI) has gained increased interest due to their excellent analytical performance and fast measurement.43,44

Affinity sensors are small devices capable of transforming a chemical signal into a physical one.45 They are known for their sensitivity and specificity by having a low limit of detection. This characteristic allowed them to be used in the detection of HMI.46 In addition, they possess many advantages as the reusability of the biorecognition molecules and a little to no sample preparation time.47
After years of development, the most remarkable affinity sensor which is currently in commercial use is the glucose AS. Figures 2 and 3 represent the different types of receptors and transducers used in the affinity sensors. Transducers are classified into three types as represented in Fig. 4. Affinity sensors are mainly composed of different types of receptors and transducers.

**Receptors**

The receptors are molecules having specificity to the targeted component. Upon their interaction with the target, the chemical or the biological reaction is transformed into a physical one, this phenomenon is called biorecognition. Aptamers, enzymes, cells, deoxyribonucleic acid (DNA), and antibodies are receptors examples.

**DNA/RNA Sensors**

As their name suggests, DNA-based sensors use single-stranded DNA molecules to detect hybrid DNA sequence targets. This allows the transducer to measure the hybridization phenomenon. This property allowed DNA-based sensors to be used in the detection of many targets biological, chemical, food, environment, and pharmaceutical. In HMI detection, a DNA functionalized iron−porphyrinic metal−organic framework (GR−5/(Fe−P)n-MOF) sensor was used in the successful detection of lead within a limit of detection of 0.034 nM. Also, it was able to detect lead in the presence of other heavy metal ions which proves its selectivity, and sensitivity.

**Antigen/Antibody Sensors**

Known as immunosensors as they use the binding of an antigen to a specific antibody in order to generate a signal, Antigen/Antibody sensors are used for diagnostics and clinical purposes as they detect biological markers that are in correlation with a disease. In essence, these sensors use Antibodies (Ab), proteins secreted by B cells of the immune system in order to target intruder proteins. These Ab possess a very high sensitivity towards their targets (also called antigens Ag) on which they bind in order to get rid of them. The binding phenomenon of Ab/Ag is described via the following reaction

\[
\text{Ag} + \text{Ab} \rightleftharpoons \text{AbAg}
\]  

For HMI detection, a monoclonal-antibodies sensor was developed for the detection of cadmium, cobalt, and lead.

The antibodies were extracted and purified from the mouse and had a specificity toward the targeted HMI. The developed KinExA device has a more sensitive detection device than the soluble cases such as microplate ELISA essay.

**Enzyme Biosensors**

The most popular enzymatic sensor is the glucose sensor, which is commercially used by diabetes patients. The key in these sensors is the usage of the enzymes of glucose oxidase (GOx) that acts as a reducing agent and thus changing the electrical components of the solution via the following equation:

\[
\text{Glucose} + \text{O}_2 \rightarrow \text{Gluconolacton} + \text{H}_2\text{O}_2
\]  

Since this reaction is oxidation the best transducer to be used in this case is an electrochemical one, with the amperometric sensors taking the center of attention.

A conductometric biosensor based on sol-gel immobilized urease integrated on a thick film electrode was developed to detect cadmium, copper, and lead. These, HMI acted as inhibitors of the enzyme having a limit of detection of 0.1 to 10 mM.

**Aptameric Sensors**

Aptamers known as chemically synthesized antibodies are nowadays the preferred receptors due to their high selectivity to the targeted molecule and small length (one-tenth smaller than antibodies). Aptamers can be used against a wide range of targets such as inorganic ions, proteins, etc. Aptameric sensors were used in the detection of HMI such as lead (Pb) and mercury (Hg) in water using electrochemical transducers with a 0.1 ng ml\(^{-1}\) limit of detection. Anti-Hg and anti-Pb aptamers were immobilized on the working electrode surface, upon interaction with their targets anti-Hg formed a hair-pinned structure, and anti-Pb formed a G-quadruplex. In both cases, the redox labels became closer to the electrode surface which allowed an increase in the electrons transfer, and thus detection of both HMI. In addition, interferences measurements were done in the presence of other ions, the sensor showed a response only for lead and mercury and no response for zinc and cadmium.

**Polymer based sensors.**—These polymers are created for the detection of a wide range of targets like inorganic and organic molecules, proteins, and pharmaceuticals. In 1992 the development of the first biopolymer sensor using chitosan and 5-formyl-3-hydroxy-4-hydroxymethyl-2-methylpyridine that was immobilized on the agarose gel to act as a fluorogenic probe. This sensor was sensitive to Zn\(^{2+}\) with a detection limit of 1 \(\mu\)M.
A decade later, a polymer-based sensor was developed for Cu^{2+} detection with a detection limit of 1.2 nM using cadmium sulfide quantum dots modified with chitosan. Many studies developed a successful polymer-based material with optical sensors for HMI detection with excellent sensitivity and selectivity and other real sensing applications in the future, some of which were successfully used for the detection of proteins.

Transducers.—Transducers can be classified into three categories: electrochemical, optical, and mechanical, Fig. 4.

Electrochemical transducers.—Electrochemical sensors involve the usage of electrodes that are applied in order to pass current into the aqueous solution where the chemical or the biological reactions happen due to the presence of the target analyte (HMI, biomarkers, etc.) and generate a measurable physical signal which is proportional to the HMI concentration, Fig. 5.

The electrochemical techniques use a setup of three electrodes constituted by the working electrode (WE), the reference electrode (RE), and the counter electrode (CE) Fig. 6. The working electrode elements can be modified with different materials for the specific detection of different types of HMI.

Carbon and Mercury were previously the first interface materials to be used for the HMI-specific determination. However, due to their instability and toxicity, Mercury electrodes are not recently used for HMI detection. Recently, a new intelligent sensor based on advanced 2D materials (A2M) was developed for the detection of HMI, Cu (II), Pb (II), Hg (II), and Cd (II) using an alkaline intercalated Ti_3C_2 within a very low detection range of 0.098, 0.041, 0.032, and 0.130 μM. These A2M sensors have advanced physicochemical characteristics, are more stable, and more intelligent having 5th generation aspects and they are as well cost-effective.

There are various electrochemical detection techniques for HMI detection noting the amperometric, voltammetric, potentiometric, and impedance. These techniques are grouped based on the electrical signal generated due to the presence of HMI in the solution.

Static technique: potentiometry.—This technique involves the measurement of the potential at current zero (no current is applied). It is a selective technique for the determination of HMI in aqueous solutions. It is used in complex mixtures for HMI detection due to its high speed, selectivity, low cost, and wide range of response. However, this technique has some limitations as reduced sensitivity and electrode miniaturization. Within this frame, nanomaterials used as WE material in combination with this technique improved its sensitivity and the detection limits of HMI.

Two main devices are employed in the potentiometric techniques: ion-selective electrodes (ISE) and ion-selective field-effect transistors (ISFET).

ISE consists of a selective polymer membrane that reduces the matrix interferences effects. Currently, the use of carbon nanostructured materials that possess excellent physicochemical properties, allowed receptors to be directly fixed on the transducer replacing the use of a polymeric membrane.

ISFETs are known to rapidly convert the chemical signal into a physical one. ISFET measures the current’s flow across a transistor that links the source to the drain.

A lot of research is ongoing in order to replace these electrodes and design safer and more specific ones such as nanoparticles, polymers, and metal oxide-based working electrode interface material.
ISFET sensors can be fabricated in a miniaturized form, thus making them usable for in-field applications.

Nano-ISFET sensors have been used for the detection of some HMI within a very low detection range.46

**Potentiostatic techniques.**—This technique involves the usage of an instrument known as “potentiostat” that controls the potential between the RE and the CE in order to maintain a potential difference between the RE and the WE as represented in Fig. 6. The resulting current is analyzed in order to know the analyte’s concentration, they are also known as controlled-potential techniques.

These techniques are sub-divided into different categories depending on the voltage signal applied and the resultant current measured.

The most basic categories are amperometry, voltammetry, and chronocoulometry.

**Amperometry.**—In this technique, a fixed potential is used in order to measure the current using a non-mercury-based electrode. The current measured will be proportional to the HMI concentration in the solution.

Because of the fixed potential on the working electrode, this technique only detects one target from an electrochemically reduced species.

Thus, the use of carbon based nano-electrode for mercury HMI detection; with a detection limit of 5 nM.66

**Voltammetry.**—Voltammetry is used to explore the electrochemical behavior of the system being studied. This method is widely used to acquire qualitative information on electrochemical reactions.

It is usually used as the primary test approach performed in an electroanalytical experiment, as it offers a fast location of redox potentials on electroactive species and evaluation of the effect of the media during a redox process.67

These techniques are used for HMI detection in complex matrices, by the measurement of current at different potential points, and to detect even trace of HMI because of its sensitivity and selectivity. Voltammetric techniques improve the detection limit by repressing the background current.46,68 Many voltammetric techniques have been developed such as cyclic voltammetry (CV), anodic stripping voltammetry (ASV), linear sweep voltammetry (LSV), etc.

**Cyclic Voltammetry**

Cyclic voltammetry can be used with spectroscopy to give information related to the reaction mechanisms of the analytes.

For the detection of HMI voltammetry is widely used because of its variability in both experimental setup and electrical flexibility.

Once the metal is present on the surface of the electrode, it sweeps between two limits E1 and E2 at a known rate also called scan rate, cyclic voltammetry is known to be a potential sweep method. When it reaches the second limit E2 it is reversed to E1 again to obtain another cyclic scan. Each CV scan is a graph of the current vs the potential also the plot indicates the potential at which the redox process occurs.

In order to have an oxidation process, a positive potential is applied that leads to a loss of an electron from the electroactive species that gives rise to an anodic peak current (ipa), leading to an oxidation peak at a given potential (Epa).

When the potential is applied in the negative direction cathodic peaks are observed (ipc) leading to a reduction peak at a given potential (Epc) as shown in Fig. 7.

**Anodic Stripping Voltammetry**

Anodic stripping voltammetry is a technique used since the 1960s for the detection of mercury. Recently, its use has increased as it has proven the ability to detect trace amounts of metals.70 The sensitivity of ASV is acquired via an electrodeposition process in which the metals present in the solution are reduced onto the electrode surface by applying a potential that is smaller than the metal’s reduction potential.71

After this process, a positive potential sweep is applied and a peak of current Vs potential is registered by the computer. The peak’s potential stands for the property of the HMI detected and the height of the peak is related to the HMI concentration.72

![Figure 6. Experimental set-up for potentiostatic measurements.](image)

![Figure 7. Cyclic Voltammogram representing the oxidation and the reduction peaks as the potential varies.](image)
ASV has many advantages noting its ultrahigh sensitivity starting with the electrodeposition process that strips the HMI, present in the solution into a very small dimension electrode which greatly improves the sensitivity of this method, also the increase of the current greatly when the reversed voltage is applied which provide excellent sensitivity improvements.

Its sensitivity is comparable to the analytical method of non-flame AAS, which has a detection limit of $10^{-10}$ to $10^{-12}$ mol.L$^{-1}$.

ASV technique is used to detect highly electronegative metals such as manganese oxide the electrochemical workstation was composed of a bismuth working electrode, Ag/AgCl reference electrode, and Au as a counter electrode.72

Figure 8 summarizes the ASV HMI detection steps.

A recent study used a new stainless-steel helical printed electrode that was electroplated with bismuth and gold for the detection of cadmium and lead HMI using ASV. This electrode showed linearity, reproducibility, and sensitivity, compared to the conventional glassy carbon electrodes used generally for the detection of these metals.73

**Electrochemical Impedance Spectroscopy**

Electrochemical impedance spectroscopy is one of the most widely employed impedance techniques for HMI detection.74

It has been used for metal detection from different biological and environmental mediums.

This electrochemical technique is very-sensitive when compared to other techniques, it is also cost-effective.

In many EIS experiments, a set sinusoidal voltage is applied by the potentiostat through a three-electrode system containing a solution of analytes to be measured. The sinusoidal voltage’s amplitude is dependent on the type of analytes under measurement.

In many cases where the measurements of impedance are performed, an electric current will flow through the electrochemical cell, this process is due to the electrochemical reactions happening on the electrode’s interface leading to a charge transfer that is recorded by the potentiostat and then converted by the software used into an impedance value when the load is applied at a set frequency.

The measurements can be given in many ways, for now, real and imaginary impedance components have plotted one another via Nyquist plots Fig. 9.

These plots are then analyzed using equivalent circuits that match the Nyquist data, this circuit includes (resistors, capacitors, and inductors) Fig. 9.

As represented in the kinetically controlled region of the Nyquist plot, charge transfer resistance (Rct) and the first point on the plot represent the solution resistance.75

A study showed the development of a sensor where they used three electrodes on a polyethylene-terephthalate-based film. Electrochemical impedance spectroscopy was used to detect various toxic HMI such as cadmium and lead nitrate at low concentrations at the nanomolar levels.76

**Experimental setup for HMI detection using electrochemical detection techniques.**—A common electrochemical setup is used for HMI detection consisting of an electrolytic cell containing the electrolyte solution and the electrode (transducer).77 The signal is measured at the electrolyte/WE interface. Inside the cell, many half-reactions occur with the target HMI at the WE interface. The reference electrode as her name implies is a reference for controlling the potential signal.46

For a three-electrode setup, the third electrode is known as the counter electrode. A general setup for HMI detection is presented in Fig. 10.

In this experiment, a three-electrode system is placed inside the electrolytic cell, and the working electrode interface can be modified depending on the metal ion to be detected. As mentioned previously the current will pass between the WE and the CE and the potential is measured between the WE and the RE.46

The three-electrode system is connected to an electrochemical workstation (potentiostat) which is a source of electrical excitation inside the electrolytic cell and measures the response related to the signals.

The electrochemical workstation will be connected to a computer containing a program that transforms these signals into a graph, curve, and numbers, these curves will give the user an accurate measurement of the HMI concentration inside the solution.

Regarding solutions with small resistance a two-electrode system consisting of a WE and RE is only required to measure the electrode’s potential Fig. 11. However, for solutions with high resistance, a three-electrode system is required in order to measure the electrode potential.46

**Optical transducer.**—As its name suggests, an optical transducer uses “light” in order to generate a signal proportional to the analyte’s concentration.

There are many categories of transducers that use light as an energy source for signal generation.

**Surface Plasmon Resonance**

Surface plasmon resonance (SPR) is a method that came to light in the last two decades due to the fact that it is a suitable and reliable

---

**Figure 8.** Anodic stripping voltammetry detection steps using a Bismuth Working electrode.72

**Figure 9.** Nyquist plot representation with the equivalent circuit and its components.
source for wide target types of detection ranging from biological molecules to HMI.

SPR happens when a photon hits the metal surface at a definite angle of incidence a part of the light couples with the electrons on the surface and causes their excitation and thus movement. The movement phenomenon is called plasmon.

The plasmon oscillation generates a 300 nm electrical field. The detection is obtained via the detector that measures light changes in the reflection. Having a low detection limit of 10 pg ml\(^{-1}\) the concentration of the target can be measured via light’s reflection intensity or by tracking the resonance angle shifts. The schematic representation of SPR sensor in the detection of the targeted analyte is represented in Fig. 12.

**Acoustic wave sensor (AWS).**—Recently micromechanical sensors found a wide range of usage, one of these usages is heavy metal ions detection. AWS works on piezoelectricity, and every fabricated sensor possesses a particular resonant frequency that is related to the width of the interdigitated electrodes and the propagation velocity of the ASW piezoelectric substrate.

The electrical signal applied on the interdigitated electrode input is transformed into an acoustic wave, flows through the piezoelectric substrate to reach the output electrode and transforms again into an electrical signal.

The absorbance of the different HMI present coated on the piezoelectric substrate is the cause behind the mass loading effect that changes the AWS velocity and thus the resultant frequency, by this way the HMI concentration can be determined.

However, these devices are not suited for usage in aqueous solutions because of the signal dispersion. Different cuts to the piezoelectric quartz material are required to acquire different signal propagation such as the ST cut are made to overcome this problem as illustrated in Fig. 13.

**Electrochemiluminescence techniques.**—Electrochemiluminescence is a combination of both electrochemical and optical techniques.

The electrochemical reactions happening on the electrode surface and the electrons transfer generates the chemiluminescence effect. This effect is generally caused by the liberation of free radicals in the solution. This technique is highly sensitive, simple, and cost-effective and is used in the detection of specific heavy metal ions.

**Microfluidics.**—Microfluidics is an arising interdisciplinary field involving chemistry, biology, microelectronics, and engineering. These devices are also known as lab on a ship because of their small size and micro-total analytical system. Impossible to be achieved with traditional techniques, microfluidics is capable of sensitively detecting a wide range of heavy metal ions, biological molecules, pharmaceutical drugs, etc.

With increased demands for on-site detection techniques, microfluidics is occupying most of the portable field analysis. At first, microfluidic devices were polydimethylsiloxane (PDMS) based, however its high- cost lead for paper and other low-cost material introduction for HMI detection. Microfluidics has many advantages such as faster reaction time, finer process control, lower...
generation waste, reagent consumption, increased system compactness, parallelization, and cost-effectiveness over traditional macroanalytical techniques.84

Electrochemical methods can be combined with microfluidics as smaller samples give accurate results, and better resolution because the ratio surface area to volume ratio of the analyte is high.70

**Sensors Developed for Lithium Ion Detection**

**Lithium bronze electrodes.**—Solid lithium bronze electrodes that are prepared from materials such as lithium vanadium bronzes (Li_V_2O_5) and lithium molybdenum bronze (Li_MoO_3) have been explored by Gadzekpo et al. Nonetheless, Li_V_2O_5 electrode was unsuccessful in lithium detection until it was integrated into polyvinyl chloride (PVC) matrix as powder. Li_MoO_3 electrode was capable of detecting lithium within a near Nernstian response and at a low concentration, but salts induced interferences Table III.85

**Conductive polymer sensors.**—Lithium-ion can be detected within a concentration range of 1 × 10^{-4} to 1 × 10^{-5} mol.l^{-1} using poly(o-methoxyaniline) polymer Fig. 14, a study by Lindino proved.

The electrochemical properties of the polymer were affected within the administration of lithium which caused a variation in the conductivity this change results in the polymer-based electrode potential change, thus a capability of lithium detection Table III.

For contact time reduction between the polymer and lithium, it has been suggested to optimize the process of flow injection.86

---

*Figure 12.* A general detection concept using Surface plasmon resonance technique.

*Figure 13.* SAW biosensor with an ST cut.
Table III. A comparison between 3 different electrodes used for the detection of Lithium ion.

| Electrode used                  | Mechanism of Li$^+$ detection                           | Lithium concentration                  | Interferences                   |
|---------------------------------|----------------------------------------------------------|----------------------------------------|---------------------------------|
| LixV2O5 + PVC powder            | Potentiometry                                            | Not very sensitive to lithium          | Salts                           |
| LixMoO3                         | Potentiometry                                            | Very low concentrations                | Nitrate or Perchlorate          |
| Poly(o-methoxyaniline)- based electrode | Change in the potential upon integration of lithium ion | $1 \times 10^{-4}$ and $1 \times 10^{-5}$ M | No interferences were mentioned |
**Ionophore-based sensors.**—In 1967 a ground-breaking study of crown ethers showed a complementarity between the macro-cycle and the bound cation. One of these cations that can be bound is lithium, lithium ionophores.

The ionophores can be integrated into the electrode surface and because of their lipophilicities, they are capable of extracting lithium from aqueous solutions into organic solvents in the preparation process for analysis.

Noting some examples of different types of ionophores in lithium detection Fig. 15. In 1977 ionophore 1 was the first selective Lithium ionophore with both characteristics of incorporation into the membrane and as an extracting agent from ethanol solution. Shortly, ionophore 2 was developed with an ion-selective solvent polymeric membrane that showed 100 times more lithium selectivity over other metal ions and 1000 times over earth cation metals. Ionophore 3 integrated cyclohexyl and isobutyl substituents over compound 2 but no increased selectivity was reported. Another trial used the chelating agent from ionophore 1 and integrated substituents found in compound 3 which resulted in ionophore 4 that showed in lipophilic membranes Li$^+$: Na$^+$ selectivity of 80:1.

Ionophore 5 had a problematic disadvantage as it was miscible with water and dissolves in organic solvents, but it was a necessary ionophore as both compound 6 and 7 structures are based on 5.

Ionophores 6 and 7 integrated dodecyl or benzyl substituents at bridgehead carbon. Compound 6, once incorporated into the ion-selective electrode was able to detect lithium in real serum samples within an average concentration range of $3 \times 10^{-4} - 3 \times 10^{-3}$ mol.dm$^{-3}$. Over 40 ionophore sensors have been developed for lithium detection such advancements will undoubtedly lead to an improved lithium-ion sensor.

**Conclusions**

Lithium is considered to be the first-line medication in the treatment of bipolar disorder as it has an effect on the suicide risk which is considered to be a major public health problem.

Lithium serum therapeutic levels are close to toxic levels, so the need for lithium monitoring has led to several detection methods ranging from the traditional analytical methods to newly developed sensors.

Considered a delicate fluid for most patients, especially the younger ones, and because of the need to accurately and frequently monitor its levels studies proved a relationship between lithium serum levels and salivary levels which shed a light on the usage of saliva during the trials in the sensor development.
However, the miniaturization and suitability for biological monitoring is still a challenging issue with these sensors. The sensors will provide an easy, fast, cost-effective, and accurate way for lithium detection, its low detection limit allowed scientists to use a non-invasive way for bipolar detection. Patients with BD will benefit from point of care diagnosis with the sensor which will ensure lithium level is in the healthy range for effective and safe treatment. With further development, the sensor can be used as a self-check mechanism such as the glucose machine used widely by diabetic patients.

ORCID

Lynn Mouawad https://orcid.org/0000-0002-1394-5304

References

1. S. Marwaha, A. Durrani, and S. Singh, “Employment outcomes in people with bipolar disorder: a systematic review.” Acta Psychiatr Scand., 128, 179 (2015).
2. A. L. Subicamanga, B. Rasche, B. Guérard, P. N. Ras, S. Hethly, N. Caiger, P. Cowen, and R. Compton, “Electrochemical detection and quantification of lithium ions in authentic human saliva using LiMn2O4-modified electrodes.” ACS Sens., 4, 2497 (2019).
3. C. Blanca, G. Laj, M. Monson, S. C. Marcus, and H. A. Pincus, “Trends in the treatment of bipolar disorder by outpatient psychiatrists.” Am J Psychiatry., 159, 1005 (2002).
4. R. W. Licht, “Lithium: still a major option in the management of bipolar disorder.” Can J Psychiatry. 13, 219 (2012).
5. P. Bebbington and R. Ramana, “Lithium: updated human knowledge using an evidence-based approach: part III: clinical safety.” CNS Drugs., 23, 397 (2009).
6. D. Gruson, K. Lallali, M. Conti, A. Legrand, A. Gruson, and P. S. Wallenmacq, “Clinical laboratory requirements for lithium assays and future of lithium assays.” Truce Elements & Electrolytes., 24, 6 (2007).
7. M. Kamenica, R. R. Kothur, A. Willows, B. A. Patel, and P. J. Cragg, “Lithium ion sensors.” Sensors (Basel), 17, 2430 (2017).
8. C. J. Metz and M. J. Metz, “An online module to understand body fluid status in clinical cases.” MedS2PORTAL., 14, 8265.17018 (2019).
9. R. K. Murray, D. K. Shy, R. M. S. M. A. Mayes, T. H. W. Rodwell, “Harper’s Illustrated Biochemistry.” (Mcgraw-hill, USA) (2014).
10. I. Miletich, “Introduction to salivary glands: structure, function and embryonic development.” Front Oral Biol., 14, 1 (2010).
11. C. Davies, “The effects of flow rate and duration of stimulation on the concentration of protein and the main electrolytes in human parotid saliva.” Arch Oral Biol., 14, 277 (1969).
12. P. J. Rieckten and T. O. Ekfo, “Demonstration of a proteolytic enzyme, salivain, in saliva.” Acta Chem. Scand., 29, 2013.1960.
13. S. More, S. Patil, M. Kakarun, R. Thakur, M. Nayan, and S. Kumar, “A quantitative analysis of total carbohydrate content from the salivary excretors in young children.” J Indian Soc Pedod Prev Dent., 36, 53 (2018).
14. V. de Almeida Pdel, A. M. Grégio, M. A. Machado, A. A. de Lima, and L. R. Azevedo, “Saliva composition and functions: a comprehensive review.” J Contemp Dent Pract., 9, 72 (2008).
15. P. Heitland and H. D. Koster, “Fast, simple and reliable routine determination of 23 elements in urine by ICP-MS.” J Anal At Spectrom., 19, 1552 (2004).
16. M. L. Chu, W. Lai, S. T. Snyder, P. K. Wong, J. C. Liao, and V. Gau, “Matrix effects—a challenge toward automation of molecular analysis.” JALA: Journal of the Association for Laboratory Automation., 15, 233 (2010).
17. V. L. Wright, M. Yelland, K. Heathcote, S. K. Ng, and G. Wright, “Fear of needles—nature and prevalence in general practice.” Aest Fam Physician., 38, 172 (2009). https://www.rrcgp.org.uk/afp/2009/march/fear-of-needles.
18. L. Cui, J. Wu, and H. Ju, “Electrochemical sensing of heavy metal ions with inorganic, organic and bio-materials.” Biosens. Bioelectron., 63, 276 (2015).
19. A. Alkhami, F. Soltani-Felegregi, T. Madrakian, H. Ghaedi, and M. Rezaeviella, “Fabrication and application of a new modified electrochemical sensor using nano-silica and a newly synthesized Schiff base for simultaneous determination of Cd2+, Cu2+ and Hg2+ ions in water and some foodstuff samples.” Anal. Chim. Acta., 771, 21 (2013).
20. C. Karunakaran, R. Rajkumar, and K. Bhargava, “Introduction to biosensors.” Biosens. Bioelectron. (Elsevier, Amsterdam) 344 (2015).
21. B. Bansod, T. Kumar, R. Thakur, S. Rana, and I. Singh, “A review on various electrochemical techniques for heavy metal ions detection with different sensing platforms.” Biosens. Bioelectron., 94, 443 (2017).
22. R. C. Marques, E. Costa-Rama, S. Wisswanathan, H. P. Nouws, A. Costa-Garcia, C. Delerue-Matos, and M. B. Gonzales Garcia, “Voltammetric immunosensor for the simultaneous analysis of the breast cancer biomarkers CA15-3 and HER2 ECD.” Sensors Actuators B: Chem., 255, 298 (2018).
23. L. Cui, J. Wu, and H. Ju, “Electrochemical sensor for lead cation sensitized with a DNA functionalized porphyrin-metal-organic framework.” Anal. Chem., 87, 138 (2015).
24. Z. Li and G. Y. Chen, “Current conjugation methods for immunosensors.” Nanomaterials (Basel), 8, 278 (2018).
25. D. A. Blake, R. M. Jones, R. C. Blake II, A. R. Pavlov, I. A. Darwish, and H. Yu, “Abnormal based sensors for heavy metal ions.” Biosens. Bioelectron., 16, 799 (2001).
26. C. Chen, Q. Xie, D. Yang, H. Xiao, Y. Fu, Y. Tan, and S. Yao, “Recent advances in electrochemical glucose biosensors: a review.” RSC Adv., 3, 4473 (2013).
27. G. Rahman and S. A. Mian, “Recent trends in the development of electrochemical glucose biosensors.” Int'l Biosens. Bioelectron., 3, 210 (2017).
28. R. I. D D. A, K. C Z, and E. Rufus, “Enzyme based biosensor for heavy metal ions determination.” Biotechnology & Biotechnological Equipment., 20, 184 (2006).
29. S. Murali, H. Kaur, N. Goswami, “Biosensors for breast cancer diagnosis: A review of bioreceptors, biotransducers and signal amplification strategies.” Biosens. Bioelectron., 88, 217 (2017).
30. H. Abu-Ali, A. Nabol, and T. Smith, “Development of novel and highly specific sialoadhesive-spanning-pancreatic elastase sensor for rapid detection of Mercury (II) and Lead (II) ions in water.” Chemosensors., 7, 307 (2019).
31. Y. Kurauchi, R. Hayashi, N. Egashira, and K. Ohga, “Fluorometric determination of zinc, cadmium and gallium ions with a fiber-optic sensor having a pyridoxal isomer-modified chitosan/agarose gel as a sensing probe.” Anal. Sci., 8, 837 (1992).
